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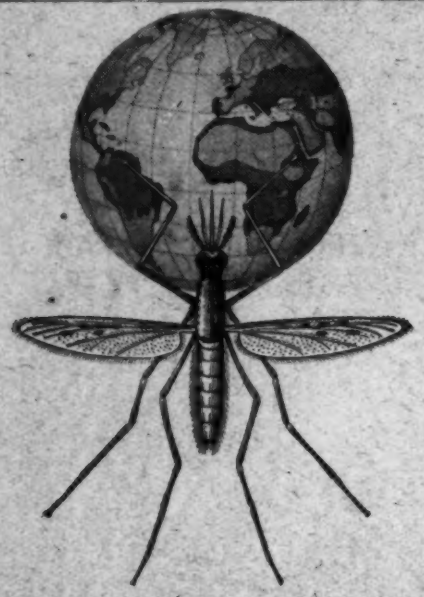

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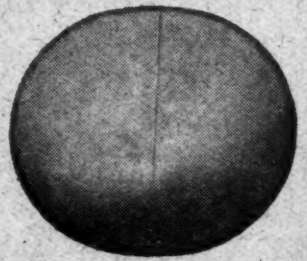

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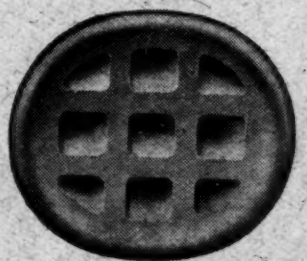

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THE PARALYSIS OF AUTONOMIC GANGLIA, WITH SPECIAL REFERENCE TO THE THERAPEUTIC EFFECTS OF GANGLION-BLOCKING DRUGS

BY

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All the activity of the sympathetic and parasympathetic nervous systems passes, on the efferent side, through peripheral relay-stations—the autonomic ganglia. Drugs which can interfere with transmission of excitation across the synapses in such ganglia must therefore influence autonomic activity profoundly and offer considerable opportunities for clinical exploitation. In the following review of present knowledge about such drugs four of them have been chosen, such that an account of them outlines the main characteristics of ganglionic block and of its potentialities.

For normal transmission in a ganglion at least two conditions must hold: acetylcholine must be normally released by the nerve terminals of the preganglionic nerve, and the acetylcholine so released must be able to excite the ganglion cell. Accordingly, paralysis of transmission may take place in several ways. First, there may be interference with the release of acetylcholine: procaine injections, or a deficiency of calcium in the fluid bathing the ganglion, can cause block in this way (Harvey, 1939; Harvey and MacIntosh, 1940). But, in general, this type of block is not at present of much practical importance. Secondly, the acetylcholine released may be prevented from acting on the ganglion cell by some drug which is itself otherwise inactive; this may be called "block by competition," indicating that such a drug acts by competing successfully with acetylcholine for receptor groups on or in the ganglion-cell membrane. Curare, tetraethylammonium, and hexamethonium are the most important drugs of this kind (Brown and Feldberg, 1936; Paton and Perry, 1951). Finally, the ganglion cell may be the site of a long-lasting depolarization, so that it can no longer give a normal response to the released acetylcholine, even though this acetylcholine is normally released and has full access to the cell. Such a "block by depolarization" is produced by nicotine and by acetylcholine itself (Paton and Perry, 1951). With block of this kind a period of excitation precedes the paralysis.

There are many drugs capable of blocking ganglionic transmission in one or other of these ways; but some of them fail to be specific and have other actions either on effector organs themselves or at other synapses. Now, upon the degree of specificity of a drug depends in large measure its usefulness. With a really specific drug, precise and accurate pharmacological and clinical investigation is possible. With a drug lacking such specificity, ambiguous results and false interpretations only too easily occur, and not a few controversies owe their origin to the existence, in a given agent, of more activities than were at first suspected. Emphasis will therefore be laid on what is required of a ganglionic-blocking agent that it may be called specific.

Nicotine

The history of ganglionic block begins in earnest in the 1890's with nicotine. It was with nicotine that Langley, having shown that it paralysed the ganglionic synapse (Langley and Dickinson, 1889), proceeded to clarify many features of the constitution and function of the autonomic nervous system. As an example of the method one may instance his work with Anderson on the ciliary ganglion (Langley and Anderson, 1892). This group of cells had been variously held to be associated with the third nerve, the fifth nerve, and the ciliary branch of the cervical sympathetic "according to the predilection of the particular observer." Langley and Anderson showed that, when the ganglion had been painted with nicotine, stimulation of the third nerve central to the ganglion no longer caused any constriction of the pupil, although stimulation of the short ciliary nerves beyond the ganglion was still pupillo-constrictor. On the other hand, excitation of the ciliary branch of the sympathetic remained effective after nicotine. The ganglion was therefore identified as an autonomic ganglion functionally in the efferent path of the third nerve, but not in that of the sympathetic fibres.

To Langley's work with this technique in mapping out the autonomic ganglia we owe much, or even most, of our knowledge of the arrangement of the autonomic ganglia. The most charming if not the most serious-minded tribute to his work in Cambridge may be quoted here:

> There was a young man of East Anglia
> Whose nerves were a network of ganglia.
> As was clear to be seen,
> He abhorred nicotine,
> Which makes ganglia Langleyer and Langleyer.

Nicotine has proved to be a reliable and fairly specific agent for blocking autonomic ganglia in pharmacological research. But there is one important point about its action which removes it from clinical use. This is the fact that it blocks by depolarization, so that its paralysing action on the ganglia is preceded by a strong stimulation. In attempting, for instance, to paralyse the ganglia controlling the blood pressure, it is necessary to pass through phases in which powerful sympathetic and vagal excitation may in turn be seen, causing a large rise in blood pressure, interrupted by a slowing of the heart, and followed by a further rise due to the release of adrenaline from the suprarenals. In animal experiments one is usually able to wait for these effects to pass before giving a further dose, and can gradually obtain the desired state of complete ganglionic block. But, for clinical practice, the necessity of passing through excitation to obtain paralysis makes nicotine (or any other drug which blocks by depolarizing) unsuitable for use in man.

Curare

When we turn to curare we come to the first of the other main group of blocking agents—those which block by competition. Curare has been used in analysing ganglionic function since the time of Claude Bernard (1857). Its use in more recent years enabled Eccles (1944) to reveal and analyse the so-called "synaptic potential," which is the electrical accompaniment of the transmission process at the ganglion synapse, and corresponds to the "end-plate potential" at the motor end-plate. Other work has shown that D-tubocurarine (or preparations owing their activity largely to this alkaloid) blocks the ganglia of the small intestine (Gross and Cullen, 1945), those controlling the blood pressure (Heymans, 1947), the vagal ganglia in the heart, and certain vascular reflexes (Burstein *et al.*, 1949). Some of these results were obtained in man, so that it seems probable that even the doses used in anaesthetic practice will have some ganglionic activity, though this should not be great.

One interesting paper describes the results of a comparison in animals of the sensitivity of different ganglia to D-tubocurarine (Guyton and Reeder, 1950); it was observed that the ciliary ganglion and the vagal ganglia were more sensitive than the ganglia supplying sympathetic fibres to the nictitating membrane, the heart, the splanchnic blood vessels, and the pupil. This is an interesting example of varying ganglionic sensitivity, which is mentioned below.

Although free from the stimulating action shown by nicotine, curare has, for purposes of ganglionic blockade, two other disadvantages. The first, of course, is that it causes neuromuscular paralysis—a feature which makes it useless clinically as a ganglionic blocking agent. Moreover, even for the pharmacologist its use presents difficulties, for it possesses a third action, that of histamine-liberation (cf., MacIntosh and Paton, 1949), which it exerts in doses not greatly different from those which block ganglia. This is a serious complication in any study of blood pressure or of blood flow, and must, of course, affect almost any analysis in which the whole animal is used.

Tetraethylammonium Ion

As long ago as 1914 Marshall described the hypotensive actions of this drug; and its mode of action, together with that of the chemically related compound tetramethylammonium, was elucidated in a classical paper by Burn and Dale in 1915. But nearly thirty years passed before Acheson and Moe (1946) and Acheson and Pereira (1946) re-examined its properties and drew attention to the possibilities of its clinical exploitation. It is chiefly to these workers and their colleagues Lyons and Hoobler that we owe the renewed interest in ganglion-blocking agents of recent years.

Tetraethylammonium is a fairly specific ganglionic inhibitor. It has not, indeed, been completely studied even now, and no one has proved, for instance, that it does not interfere with the release of acetylcholine. But there is no doubt that the bulk of its actions are those of ganglionic blockade and that it lacks any stimulant action on ganglia. It has been shown to block the superior cervical ganglion, the ganglia supplying the nervi accelerantes of the heart, the vagal ganglia to the heart, those supporting vasomotor tone and mediating vascular reflexes, those of the pupil, the stomach, the bladder, the salivary glands, the small intestine, the sweat glands, and the splanchnic nerves to the adrenal. Studies of this kind have established that it is a valuable tool to the pharmacologist and, for diagnostic purposes, to the clinician.

The actions of tetraethylammonium, however, are relatively transient, and its potency is not very high. Further, it has other side-actions of an interesting (and puzzling) nature: (1) the paraesthesiae and metallic taste experienced by patients after intravenous injection: (2) the ability to cause repetitive firing in frog nerve and hence fibrillary twitchings in muscle (Cowan and Walter, 1937); (3) the ability to cause muscular paralysis in some patients (Burt and Graham, 1950); and (4) the ability to evoke the secretion of adrenaline (or a related substance) from the liver and adrenals so that it actually causes, under some conditions, a rise in blood pressure (Page, 1949).

Of these side-effects the fourth in particular seems to be a possible source of confusion. The other side-actions—paraesthesiae, fibrillations, and muscular paralysis—may be clinically undesirable, but these effects are at least easily distinguishable from those attributable to ganglionic paralysis. It is much harder, however, when faced with the result of an injection of tetraethylammonium, to be certain how far the total effect observed is due solely to autonomic blockade and how far it is modified by adrenaline secretion. Thus the tachycardia observed after an injection of tetraethylammonium in man, the failure of attempts to select patients for sympathectomy according to their response to tetraethylammonium (Soloff, Burnett, and Bello, 1948), the ability of tetraethylammonium to lessen the gastric secretion in response to histamine and to urecholine (MacDonald and Smith, 1949; Robertson *et al.*, 1950), and the reduction of renal blood flow and of urine flow during a water diuresis by tetraethylammonium (Aas and Blegen, 1949) are all observations whose interpretation needs care if there is a possibility of an increase in circulating adrenaline.

But, although tetraethylammonium has not proved entirely satisfactory for producing clinically a specific and long-lasting ganglionic block, its use has demonstrated the importance of ganglion-blocking agents, and its deficiencies must not be taken as a failure of the ganglion-blocking technique.

Hexamethonium

This compound ($N^+(CH_3)_3.(CH_2)_6.N^+(CH_3)_3.$) is one of the methonium series, in which pharmacological activity varies sharply with the number of carbon atoms in the methylene chain joining the terminal quaternary groups (Paton and Zaimis, 1949). The properties of hexamethonium (C6) are also (in general) those of pentamethonium (C5) and tetramethonium (C4), and are described in detail by Paton and Zaimis (1951): for brevity I will refer only to hexamethonium unless there is some particular distinction to be drawn.

For the analysis of effects of hexamethonium on ganglia, the cat's superior cervical ganglion is still an unrivalled test object, using as a record of its activity the contraction of the strip of smooth muscle in the orbit called the nictitating membrane (to which some of its post-ganglionic fibres run). With this preparation excitation of the preganglionic nerve at 10 shocks a second causes a sustained contraction for many minutes or as long as an hour. This contraction is temporarily weakened by agents paralysing transmission through the ganglion, and it may be used for quantitative comparisons.

Proof of Ganglionic Block by Competition

But more elaborate tests must be done to determine whether it is indeed ganglionic block that is occurring. That hexamethonium has not affected the power of the nictitating membrane to contract is shown by injecting adrenaline (which excites the membrane directly) before and during a paralysis by hexamethonium; the contraction to adrenaline is unaltered in the presence of a fully paralysing dose of hexamethonium. That the nerve trunk running from the ganglion to the membrane has not been attacked is shown by stimulating it before and during the effects of a dose of hexamethonium and comparing the result with that of pre-ganglionic excitation. Although pre-ganglionic excitation becomes ineffective, post-ganglionic excitation is still fully effective. But it might still be that the pre-ganglionic trunk, or its delicate nerve terminals, is attacked. This is tested by perfusing the ganglion and determining whether the release of acetylcholine by excitation of the pre-ganglionic nerve persists in the presence of hexamethonium. Even with the injection of a large dose of hexamethonium exclusively into the ganglion perfusion system, acetylcholine is still normally released. Finally, it was observed that the ganglion was not depolarized during the action of hexamethonium and that the paralysis was never preceded by excitation (Paton and Perry, 1951).

Effects on the Blood Pressure

The effects of hexamethonium on the cat's blood pressure are of particular interest, with reference to its use in hypertension. A dose of 1–2 mg./kg. usually produces a moderate fall of blood pressure; but further doses, up to 20–30 mg./kg., produce no further effect. At the same time, the effects of nicotine (a stimulant to the vasomotor ganglia) are abolished, but the effects of acetylcholine and adrenaline are not reduced. Such an experiment (which could equally well be done in man) shows: (1) that the actions of hexamethonium on the blood pressure are exerted only by the release of autonomic tone, and not by any direct vascular action; (2) that it has no other depressor effect even in large doses; and (3) that it has no atropine-like or "adrenolytic" action.

The actions of acetylcholine and adrenaline are, however, altered. The depressor effect of acetylcholine is prolonged (although hexamethonium is free of anticholinesterase activity); and the pressor effect of adrenaline is both increased and prolonged. These effects are no doubt due to the paralysis of the compensating mechanisms normally maintaining the constancy of the blood pressure. Similar observations have been made with tetraethylammonium (Page and Taylor, 1947). When using ganglion-blocking agents, therefore, it is necessary to remember that the response to drugs and procedures affecting the blood pressure will necessarily be exaggerated, as the mechanisms maintaining a normal blood pressure are weakened.

The pharmacological study of hexamethonium, in short, has shown it to be a specific ganglion-blocking agent of low toxicity, and to be free from other properties such as stimulation of nerve terminations, ganglia, striated muscle or smooth muscle, neuromuscular blocking action, atropine-like action, histamine liberation, or anticholinesterase activity (all of which have been found in other quaternary compounds in association with the power to block autonomic ganglia). For such reasons it was proposed for clinical trial (Paton and Zaimis, 1948).

Sensitivity of Different Ganglia

Hexamethonium is not equally active on all autonomic ganglia. Of those ganglia tested in animals hitherto, it appears that the parasympathetic ganglia to the salivary gland are the most sensitive, then the superior cervical ganglion, the vasomotor ganglia and visceral ganglia, and the vagal ganglia in the heart, in turn. This "spectrum" of ganglionic sensitivity seems to vary with each ganglion-blocking agent. Thus tetramethonium has more and pentamethonium less effect on the intestine relative to their effects on the superior cervical ganglion than has hexamethonium. Tetraethylammonium, too, causes for equal hypotensive effects a much greater paralysis of ocular accommodation than does hexamethonium. The work of Guyton and Reeder (1950) with curare, already quoted, provides further examples of the same phenomenon of varying ganglionic sensitivity. The reasons for this variation are still entirely obscure, and the sensitivities of different ganglia to different drugs must each be determined individually. Nevertheless, these observations offer a hope of eventually obtaining ganglion-blocking compounds more or less adapted to particular ganglionic systems.

Potency and Ganglionic Activity

A characteristic of a muscle partially paralysed by curare is that, while a single shock to its motor nerve may yield a quite vigorous twitch, with repeated stimuli the tension rapidly falls away—that is, a curarized muscle cannot hold a tetanus. The most likely explanation for this is that the acetylcholine output at the junction falls as stimulation proceeds. Normally this does not matter, as considerably more acetylcholine than necessary is released; but in the curarized muscle, whose threshold to acetylcholine is raised, the fall in output can reveal itself in a deepening neuromuscular block.

It is probable that a similar situation exists with pentamethonium or hexamethonium. It is known that the acetylcholine output from a perfused ganglion undergoing continuous stimulation falls with time.

Corresponding to this, after a suitable dose of hexamethonium, a pre-ganglionically excited tetanus of the nictitating membrane, which previously produced a well-sustained contraction, now produces a spiky contraction, which at first is not far in height from the control, but which cannot now be maintained. Thus, as stimulation is prolonged, the ganglion becomes more sensitive to the blocking agent. In the same way, if high rates of stimulation are used the ganglion is more sensitive to the blocking agent than with slower rates; this fact can be made use of in assaying small amounts of the drug.

These effects, by which intense or prolonged activity alters the state of the ganglion and increases the action of pentamethonium or of hexamethonium, are relevant clinically. They may explain why it has been possible to give doses relieving hypertension or ulcer pain without paralysing, say, the normal function of the small intestine and bladder. For if one makes the assumption that in hypertension the vasomotor ganglia are hyperactive (or, in ulcer, the ganglia of the stomach), then it should be possible to diminish this overactivity considerably before interfering with the quieter-paced normal function.

Further, if this is true then the proportion of side-actions to therapeutic effect will be least in the truly functional disorders. On the other hand, in those conditions in which there is no specific overactivity of this sort, in which any effect produced is due to the paralysis of some normal function, side-actions may be expected to be more severe. It may be possible, therefore, to infer from the intensity of side-effects whether the action of hexamethonium in a given disease is through the relief of an abnormal autonomic pressure, or whether it is simply that the reduction of a normal autonomic function happens to provide some palliation of the disorder.

Effects of Hexamethonium in Man

The first trials (actually carried out with pentamethonium) (Organe, Paton, and Zaimis, 1949) served to establish the primary fact that the order of activity of these drugs was roughly the same in man as in the cat (in which most of the analysis of their action was done). Since then much valuable information has been gained, chiefly in the two fields of cardiovascular and gastric function.

Effects on Normal Blood Pressure and in Hypertension

Arnold and Rosenheim (1949) and Arnold, Rosenheim, and Goetz (1949) showed that pentamethonium lowers the blood pressure to a degree comparable to, and sometimes greater than, that by sedation or by tetraethylammonium; that with this is associated a warming of the skin of the lower limbs and an increase in digital blood flow; and that adrenaline is still fully effective in the presence of pentamethonium.

Burt and Graham (1950), in a quantitative analysis of these vascular actions, confirmed and extended these findings. They found that the effects of pentamethonium and hexamethonium were associated with an increase of limb blood flow, and that this increase was greater, more regular, and longer-lasting in the lower limbs than in the upper limbs, although vigorous reflex vasodilatation of the upper limb could be obtained. The paucity of the response of the upper limb is a curious observation, about which one can only speculate. Sweating was also investigated, and was depressed by both drugs in those cases in which a rise in skin temperature was elicited. They have also observed paralysis of the bladder (by cystometrogram) and abolition of movements of the small intestine studied through an ileostomy.

Lately, several more studies of the actions of hexamethonium or pentamethonium have been initiated by Turner (1950, 1951), Saville (1950), Campbell and Robertson (1950), Mackey (1950, personal communication), Smirk (1950, 1951), Frankel (1951), Locket (1951), and others, bearing more directly on its use in hypertension and toxaemia of pregnancy. This is all recent and current work, and it is perhaps still premature to do more than outline its character. There is no doubt, however, that regular oral doses of pentamethonium and hexamethonium can in many cases cause a substantial fall in blood pressure, which may be maintained for weeks or months. With this fall there is usually relief of such symptoms as headache, dizziness, ocular disturbance, and breathlessness on exertion. Further, there have already been indications that the physical signs of hypertension, particularly in its so-called "malignant" phase, may actually regress. There may be disappearance of papilloedema, diminution of heart size, and improvement in renal function. There is tentative evidence that some of these benefits may persist after ceasing to give the drug, suggesting that it may succeed in interrupting the "vicious circle" postulated by Byrom and Wilson (1939).

These results are promising. But it seems probable that the action of these drugs in hypertension will not be fully exploited until another property displayed by them is analysed: the ability, reported by all workers, of causing postural hypotension.

Postural Hypotension

For a substantial time after an injection, after any effects on the supine blood pressure have passed, profound falls in blood pressure may be obtained in some subjects if the subject stands quite still for a few minutes. This is indeed the only important difficulty in using hexamethonium clinically, although it is not yet clear how seriously it should be regarded. Two facts make it questionable whether this hypotension is due simply to relaxation of control of arteriolar tone: the first is that it outlasts the effect on the supine blood pressure; the second, that exercise promptly relieves it. The latter observation brings forcibly to mind the venous pump mechanism actuated by the muscles, and raises the question whether there is not rather some relaxation of venous tone involved.

A similar conclusion is suggested by Enderby's (1950) stimulating observation that a patient with a systolic blood pressure lowered by pentamethonium or hexamethonium to a level of 60–70 mm. Hg is in an excellent state for many surgical operations (particularly those of the ear, nose, and throat or of the plastic type); for under these conditions bleeding is minimal yet tissue oxygenation and nutrition are said to be fully preserved. These results have now been amplified (Enderby and Pelmore, 1951) and confirmed (Hughes, 1951). It is difficult to believe that bleeding would be lessened if such a fall in blood pressure was achieved solely by arteriolar dilatation; but hypotension due to the accommodation of blood in relaxed venous reservoirs would be quite compatible with a dry operative field. It appears, in short, that the postural

hypotension and the dry surgical field caused by hexamethonium indicate that one of its actions is the relaxation of a venomotor tone. There is little physiological evidence to support the existence of a sympathetic tone of this kind; but if it does exist it must influence considerably our views of how hexamethonium acts, how it should be used in hypertension, and how postural hypotension as a side-action is to be minimized.

Effect on Gastric Activity

We owe to Kay and Smith (1950a, 1950b) the studies of the action of hexamethonium on gastric function. These workers have shown decisively that intramuscular doses of hexamethonium will inhibit spontaneous secretion of hydrochloric acid to the point of achlorhydria, will reduce the volume and acidity of spontaneous night secretion of gastric juice, and will inhibit the motor activity of the intestine and relieve ulcer pain when this is present. They also find that it reduces the gastric secretion to insulin-induced hypoglycaemia, but does not affect the response to histamine. They have continued their studies, using larger doses by oral administration, and have found a similar reduction in gastric secretion. Hexamethonium has also been shown radiographically to reduce the emptying time of the stomach considerably, and to lessen the mobility of the duodenum and jejunum (Douthwaite and Thorne, 1951). It is clear from this work that hexamethonium is potentially important for the treatment of peptic ulcer. A hopeful beginning has already been made (Scott, Kay, O'Hare, and Simpson, 1950) on the difficult task of establishing whether it does in fact accelerate healing of peptic ulcer as well as relieve pain. But it is still uncertain, for instance, whether such beneficial effect is due to depression of acid gastric secretion or to depression of gastric and intestinal motility.

"Side-actions"

Bromism and iodism can be avoided by the use of non-toxic salts of hexamethonium (Paton and Walker, 1951; Campbell and Robertson, 1951). The technique of diminishing undesired elements of the syndrome of ganglionic block (arbitrarily termed "side-actions" is still developing. Severe ileus should not be allowed to persist: neostigmine is effective (Bourne and Hosford, 1951). Fall in blood pressure may, in view of Enderby's results, be less hazardous than it appears. Postural control is obviously of prime importance, but control of blood pressure by sustained infusions of adrenaline has nothing to recommend it: "adrenaline shock," which may be lethal, has been known for over 30 years (Blackett, Pickering, and Wilson, 1950).

Future Work

The actions of hexamethonium in man hold therapeutic promise and, as one reviews them, are all attributable solely to ganglionic block. With this promising beginning, one turns to consider future lines of progress. There is, of course, a great deal of work to be done in confirming the results already obtained and comparing their therapeutic uses with established procedures. It is only two and a half years since these compounds were proposed for clinical trial; and the technique of their use, like the techniques of using curare or digitalis, has still to be evolved.

One looks forward to an analysis of the haemodynamics of the circulation in man after hexamethonium; the extension of the use of the drug to other clinical conditions involving autonomic activity; the study of combinations of a ganglion-blocking agent with a drug exciting, say, that part of the autonomic nervous system whose activity it is desired to retain. Physiologically, there are many details of the blocking process to be elucidated. Further, without doubt other blocking drugs will be developed whose actions will require analysis, although it is doubtful if any of them will be so simple chemically as hexamethonium; there are, indeed, many already recorded in the literature worthy of study.

Use of Hexamethonium for Clinical Research

Perhaps the most important aspect of hexamethonium is that it provides a potent and specific tool for analysing autonomic activity. Whatever the therapeutic uses of such a drug, in the long run one of its most valuable features will be that it allows a direct experimental attack on that much abused word "functional" and such relatives as "vagotonia" and "autonomic imbalance," so often attached to a disorder "according to the predilection of the particular observer." Langley and his colleagues were able to use nicotine to analyse the structure and function of the autonomic nervous system in animals; their work was essentially that of defining the autonomic connexion between normal activity in normal organs and the central nervous system.

We can now extend this study to clarifying how far certain abnormal activities in normal or abnormal organs originate in the central nervous system and are mediated through the autonomic nervous system. In physiology, indeed, hexamethonium is already proving a useful weapon; thus Feldberg (1950) has been able to analyse satisfactorily the action—which had recently been called in question—of substances such as acetylcholine, histamine, and barium on the small intestine, and to show that barium (so long regarded as a specific stimulant to smooth muscle) in fact has a powerful ganglionic stimulating action. Likewise, Kay and Smith (personal communication) are already finding that ulcer cases may be divided according to their response to hexamethonium; there is no need to point out the possible importance of such a division.

As a tool, however, neither hexamethonium nor any other ganglion blocker is useful unless it is specific. It is possible, of course, that a particular side-action may be, for a particular disorder, useful rather than otherwise. One could quote the compound "banthine" (Longino *et al.*, 1950) to illustrate this. This is stated to have both a sympathetic ganglion-blocking action and a somewhat more intense atropine-like action; such a combination might be a convenient mixture of properties. But at the same time this makes it very difficult to discover whether the drug has any action on *parasympathetic* ganglia, for the effects of block of these have already been produced by the atropinic postganglionic block. In the words of Longino *et al.*, "The amount of drug necessary to block parasympathetic synapses could not be determined by the methods employed." For all one can tell from the evidence so far, there may be no such parasympathetic block exerted in the tolerated dose range of the drug. Whatever the usefulness of such a drug in treatment, it is clear that its use can tell us little more about, say, gastric ulcer than we have gained from experience with atropine itself. For reasons of this kind, an attempt has been made to emphasize the value to be attached to the specificity of a ganglion-blocking drug.

One may end on a frankly physiological and even more frankly speculative note. The physiological interest of ganglia lies particularly in their relation to the other two synapses—the motor end-plate between nerve and muscle, and that between nerve cells—the central nervous synapse. A longer-chained member of the methonium series, decamethonium, acts only at the myoneural junction. Next to this there are pentamethonium and hexamethonium, closely related to decamethonium but acting only at the ganglionic synapse. May not this be a pointer to yet other compounds specific for the central nervous synapse? And if there are, may there not be, as with ganglia, degrees of specificity within the central nervous system? It is engaging to consider what sorts of action one might expect from such drugs. One thing, at least, seems certain—that the synapse in its various forms has many problems and surprises in store for both clinician and physiologist.

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METHONIUM COMPOUNDS IN THE TREATMENT OF HYPERTENSION

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In the past year the ready availability of pentamethonium and hexamethonium bromides has resulted in their liberal use in the treatment of essential hypertension and hypertension due to other causes, such as nephritis and toxaemia of pregnancy.

Paton and Zaimis (1949), Organe, Paton, and Zaimis (1949), Arnold and Rosenheim (1949), and Arnold, Goetz, and Rosenheim (1949) used the pentamethonium compound in view of its more selective sympatholytic action and therefore the greater possibility of avoiding parasympatholytic side-effects.

Arnold and Rosenheim (1949) and Arnold, Goetz, and Rosenheim (1949) found that pentamethonium iodide produced a fall in blood pressure comparable to that of tetraethylammonium chloride, but the required dose of the former drug was much smaller and in general its action was somewhat more prolonged. Hypertensive symptoms such as headache were relieved in an occasional case for as long as eight hours.

Burt and Graham (1950), using the pentamethonium and hexamethonium iodides intravenously in doses of 30 to 40 mg., were able to produce falls in both systolic and diastolic blood pressure for as long as 95 minutes.

More recently, optimistic views have been expressed in the use of these drugs for the long-term treatment of hypertension based upon small series of cases. Campbell and Robertson (1950) report that they treated eight cases of severe hypertension with hexamethonium bromide, and all the patients showed a marked lowering of blood pressure and relief of symptoms. Two features of their paper are worth particular notice: first, that apparently the drug was given orally only in four cases, with results equalling those when it was given by injection, and, secondly, that several of their cases maintained an almost normal blood pressure for some time (two months in one case) after the drug was discontinued, and the patients were being seen as outpatients. However, an occasional failure is reported (Freeman, 1950) in spite of 600 mg. a day given by injection and as much as 10 g. a day orally. Complications so far reported are ileus and its resulting constipation, and also vasomotor collapse, which is said to respond dramatically to intramuscular ephedrine. No deaths have yet occurred, though coronary and cerebral thrombosis are theoretical possibilities.

This paper is a report on the use of either pentamethonium bromide or hexamethonium bromide in 34 cases of essential hypertension and continuing

observations on 38 patients during the same period. In two cases—L.M. and E.H. (Table VI)—both drugs were tried.

Material

All the patients attended the out-patient department of this hospital with symptoms directly referable to their hypertension. There was one case of malignant hypertension, two patients who had had bilateral sympathectomy with little or no improvement, and others with hypertensive encephalopathy, congestive heart failure directly due to hypertension, paroxysmal nocturnal dyspnoea, severe headaches, and vertigo. Many of these patients had been attending this hospital for some years for their hypertensive symptoms, and a few had been in-patients. Most of the patients were women (25 females to 13 males). The youngest patient observed was a 16-year-old youth, the youngest patient treated with the methonium compounds was a woman aged 39, and the oldest patients treated were a woman and a man aged 70. The average age of the treated female patients was 53 years, and of the males 59 years.

Investigation of these cases did not reveal any evidence of nephritis, coarctation of the aorta, phaeochromocytomata of the adrenal gland, or any cause for the hypertension other than what is known as essential or malignant hypertension.

The procedure adopted in each case was the same. The patients were put to bed, and for a fortnight the standard treatment for their condition was given, excluding the use of the methonium compound. In every case this initial treatment was continued when the patient was put on a methonium compound. Biochemical investigations, renal-function tests, electrocardiography, and radiological examination were carried out in every case. However, much of this information is not relevant to the present inquiry and is therefore not considered.

TABLE I.—*Showing Height of some Serum-bromide Levels in Relation to Number of Weeks after Starting Treatment*

Cases:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
End of 1st week ..		Neg.															15					
.. 2nd	25		25		20	Neg.	25		25	Neg.		60	30	30		35	40	25		60		25
.. 3rd											35				50		75			55		
.. 4th	75	60		100				75	50			75					60			65	75	50
																	100					
.. 5th			50		25							75					100		40			
.. 6th	80					75				50			25				90					60
.. 7th		75	60	75	55				35		100						75		100			
.. 8th										75							70				75	60
.. 9th							25															40
.. 11th											50											
.. 13th		30																			75	

Cases 4, 7, and 8 were receiving pentamethonium bromide, the others were receiving hexamethonium bromide. The drug was stopped in Cases 2 and 11 at the 7th week, in Case 8 at the 8th week, and in Case 17 at the 5th week.

TABLE II.—*Patients Receiving Pentamethonium Bromide. The Periods in this Table Apply to Tables III, IV, and VI also. Blood Pressures are Averaged Over Two-day Periods Except for Period III, when they Represent O.P. Figures at Two- or Three-weekly Intervals. During the Early Part of Period II Patients were still Spending Part of the Day Resting in Bed*

Case	Period I: Control Resting in Bed	Period II: Receiving Drug in Hospital by Intramuscular Injection at First, and Later Orally	Period III: Attending as an Out-patient Receiving Drug Orally Only
F.L.	253 255 233 233 233 243 180 145 145 143 150 155 150 140	195 215 210 220 205 215 220 220 225 230 115 125 130 125 128 123 133 145 147 153	260+ 260+ 170 175
A.J.	240 235 245 235 220 225 165 165 150 143 140 125	225 215 200 190 185 175 200 185 190 200 130 133 125 120 125 123 120 123 123 118	260 235 260 150 145 150
E.B.	200 187 190 190 187 183 120 115 110 110 117 110	175 167 165 155 145 155 150 135 155 155 107 105 103 100 97 97 97 97 100 100	167 175 200 110 130 135
M.J.	190 185 173 195 200 185 195 100 95 95 100 97 103 90	143 140 168 130 150 143 145 160 175 195 87 83 85 80 83 83 87 90 85 100	210 187 190 110 100 110
F.C.	170 170 165 170 175 170 115 97 95 95 100 93	145 145 140 137 145 140 125 87 90 95 87 85 87 87	Refused to continue with C5
F.E.	240 228 196 210 189 185 123 110 110 113 107 110	153 154 135 134 133 135 138 133 142 141 90 88 80 85 80 75 80 88 80 89	Refused to continue with C5
T.B.	215 200 215 213 185 192 176 126 133 155 143 118 124 113	167 178 174 167 165 177 177 165 187 175 114 122 115 117 120 112 108 113 116 118	260+ 220 240 155 150 150

In each pair of figures the upper represents average systolic pressure and the lower is average diastolic pressure.

TABLE III.—*These Patients all Developed Complications Recorded in the Text*

Case	Period I	Period II	Period III
H.H.	270 265 265 253 258 257 245 148 143 135 132 132 133 135	217* 232 230 215 210 190 216 211 128 135 130 125 126 130 135 135	240 240 220 225 160 150 150 145
F.E.	240 240 160 160	0* 0	Died
J.W.	180 175 168 173 175 163 193 122 120 113 108 102 105 125	160 172 161 180 182 172 176 168 172 168* 90 100 107 112 112 103 103 103 100 95	
A.L.	200 190 183 177 165 172 167 100 95 90 75 83 82 82	150 135* 155 155 160 160 160 165 165 160 75 85 83 82 81 77 70 80 77 77	
T.H. (2) ..	260 270 220 220 260 241 228 140 135 120 130 150 152 127	240 245 260 190 270 270+263 270+270+240 126 128 110 114 160 164 170 185 178 160	Developed bromide poisoning after 7 weeks of C6

* Indicates the approximate time that the complication developed and the drug was stopped.

TABLE IV.—*Patients Receiving Hexamethonium Bromide*

Case	Period I	Period II	Period III
L.F.	240 203 208 185 203 205 200 130 130 140 120 127 143 120	172 172 170 165 166 170 155 177 170 112 112 110 107 108 110 115	235 195 220 230 125 100 130 140
M.M.	230 210 200 192 177 185 182 110 110 112 108 106 104 108	163 163 158 155 153 150 153 160 170 165 95 100 90 95 110 105 100 95 95 97	230 220 230 240 240 130 120 127 140 136
A.Do.	205 195 183 175 167 165 167 110 107 104 100 95 110 110	150 145 155 160 150 155 165 162 175 175 105 90 100 100 107 105 102 100 102 104	175 180 190 125 115 130
A.D.	195 180 175 170 167 155 147 112 105 102 100 95 97 105	153 147 143 153 155 95 105 106 97 95	260 223 238 250 120 130 135 125
J.C.	190 187 187 187 185 175 115 130 115 113 110 110	157 153 165 170 160 163 177 178 108 112 115 110 110 109 105 110	190 210 220 230 115 120 127 135
A.S.	165 150 150 140 130 120 140 110 105 100 75 87 95 95	130 130 135 135 115 125 140 97 93 95 100 95 95 105	170 150 175 180 120 100 115 120
G.J.	185 180 180 170 180 125 118 112 112 113	153 170 155 170 160 170 180 190 105 115 104 109 110 112 120 130	200 200 115 130
E.U.	255 250 247 247 252 245 240 146 149 150 145 155 151 145	240 243 252 247 244 240 250 246 249 247 145 151 155 153 148 151 153 152 150 150	250 265 270+ 270+ 270+ 210 130 150 140 155 165 135
T.H.	255 235 230 232 230 240 235 140 135 137 140 143 144 145	215 223 210 233 232 235 233 240 230 125 127 131 130 141 135 145 127 132	270+ 240 190 250 160 120 120 140
J.B.	205 205 223 228 230 236 238 100 120 121 130 127 132 131	240 246 252 245 243 250 256 250 255 100 130 120 124 122 102 130 132 131	235 240 260 125 120 140
W.M.	210 200 157 175 162 165 175 150 125 110 100 102 112 110	175 177 182 175 156 156 180 175 110 112 107 112 105 110 117 125	Did not attend further

TABLE V.—*Group of Controls. No Treatment other than Rest in Bed*

Case	Rest in Bed	Up and About in Ward	Seen in O.P. Department
W.P.	220 195 157 160 145 150 140 120 110 107 108 103 98 96	138 145 147 144 150 146 144 144 95 95 97 93 95 97 90 87	150 175 215 105 110 125
A.P.	200 185 177 172 170 165 160 143 125 115 112 100 103 102	162 150 152 151 160 165 150 110 90 85 87 95 100 95	
P.M.	210 175 150 151 153 145 127 125 110 95 105 90 92 90	150 128 130 125 130 115 90 85 85 80 80 75	155 190 240 100 120 125

TABLE VI.—*Combined Hexamethonium and Pentamethonium Bromide*

Case	Period I	Period II		Period III
		Pentamethonium Given	Hexamethonium Given	
L.M.	208 232 240 217 200 220 195 140 143 147 142 135 130 133	180 177 175 187 175 187 178 210 115 105 108 105 105 110 120 110	220 170 171 173 174 190 195 200 205 107 109 108 110 120 125 120 119 118	270+ 230 240 240 145 130 140 140
E.H.	175 160 150 155 180 185 200 125 120 115 110 105 120 123	175 165 163 150 155 148 163 164 112 110 105 108 105 107 105 104	164 145 135 150 160 155 170 110 110 105 110 105 110 112	210 220 225 225 130 132 125 130

During the first two weeks in hospital the blood pressure was taken several times daily, and this procedure was continued as long as the patient was in hospital. In many cases the blood pressure was taken twelve or more times daily, and seldom fewer than four readings a day.

The accompanying tables show the average blood pressure for every two days. This method of recording the results was necessitated by the impossibility of reproducing the charts of every patient, though graphs show the results much more dramatically and convincingly. It should be emphasized that this method of recording would favour the methonium compound even were it of little or no value in the prolonged treatment of hypertension. The immediate sudden fall of blood pressure after an injection, though only temporary, lowers the average for the day (as readings are taken before and usually within an hour after injections) and shows an apparent advantage in the use of the drug for *prolonged treatment* when in fact no such advantage exists. However, discontinuation of the drug would result in an immediate loss of this apparent advantage, unless the blood pressure had been effectively and persistently reduced for several days or more. Nor do these tables reveal the marked variation in blood pressure that may occur in any single day in hypertensive patients with and without treatment.

Initially the drug was given by intramuscular injection. The dose ranged from 25 mg. to 150 mg. intramuscularly at intervals of from two hours to six hours, the time interval of injections being decreased and the dosage increased according to the response of the patient. In some cases the intramuscular dose had to be rapidly increased as the patients developed a tolerance for the drug. After two weeks of injections the drug was given by mouth, injections being discontinued, and after 24 to 72 hours the patient was allowed up and gradually given the full run of the ward. We felt that 250 mg. by mouth was an approximate oral equivalent to an injection of 50 mg., but nevertheless the acute fall in blood pressure which followed an intramuscular injection did not occur after even large oral doses. With increasing experience in the use of the drug the period of injections was reduced often to ten days or less. What this increasing experience indicated is discussed later. The oral dose was 500 to 1,000 mg. of pentamethonium bromide four- or six-hourly, or 250 to 500 mg. of hexamethonium bromide, increased until

it was given as frequently as every two hours. The oral dose which these cases received as out-patients usually exceeded a total daily dose of 3 g. of hexamethonium or pentamethonium bromide taken evenly divided at two- or three-hourly intervals. Most of the patients continued to attend at weekly or fortnightly intervals. Several discontinued the drug on their own accord, and when they attended volunteered the information that they felt better without it. Some others discontinued the drug and did not attend further. In fairness we must say that almost all those who continued taking the methonium compound claimed partial or complete relief of many of the symptoms for which they originally attended, particularly when their complaint primarily was of headache, dyspnoea, or vertigo, even when we could record no appreciable fall in their blood pressure or objective improvement.

Methods

Determination of Serum Bromide.—The concentration of bromides in the serum of the patients was determined by the gold chloride method. In this method the proteins of serum are precipitated with trichloracetic acid and an aliquot of the filtrate is treated with 0.5% gold chloride solution. With bromide, gold chloride yields a double salt of a deeper yellowish-brown colour than that of the added gold chloride solution: the colour is then compared with that of a series of bromide standard solutions similarly treated, and the result is expressed as milligrams of sodium bromide per 100 ml. of serum.

Determination of the 17-Ketosteroids of Urine.—The 17-ketosteroids in the urine of the patients were determined by quantitative application of the Zimmermann reaction as described by Callow, Callow, and Emmens (1938). An aliquot from a 24-hour specimen of urine is hydrolysed by acid and the steroids are set free from their water-soluble conjugation and extracted with ether. Phenolic and acidic impurities are removed by washing with alkali, and the neutral ketosteroids are determined, after removal of the ether, by colour reaction with a solution of *m*-dinitrobenzene in alcohol, due allowance being made for reagent blanks.

Findings

It is unnecessary to record the details of our results for each case, as the information is presented in the tables. We have not produced figures for every patient, but those few omitted differed in no way from the 28 whose results are recorded.

During the initial fortnight in bed in most cases both the systolic and the diastolic blood pressure fell, and in some to normal limits in a few days. We must again emphasize that most of these patients were known hypertensives of long duration who had been attending either this hospital or their own doctor for some few years, and the lability of their blood pressure bore no relation to their age. This initial fall was so marked that in three cases—W.P., A.P., and P.M. (Table V)—we did not give the methonium compound, but thought it would be interesting to note how soon ambulation would elevate the blood pressure to its previous level. These patients were allowed up after the third week and given the full run of the ward. It is important to note that the blood pressure kept down for the remainder of their stay in hospital, but was up to hypertensive levels when they were seen again as out-patients.

It might also be emphasized here that papilloedema *alone*, in spite of statements to the contrary (Evans, 1948), is not a criterion of the presence or onset of malignant hypertension. Malignant hypertension can exist without papilloedema, and papilloedema may occur in essential hypertension and disappear without any treatment producing a fall in blood pressure (Goldring and Chasis, 1944; Osman, 1950). Hence its disappearance cannot alone be used as indicating the success of any particular therapeutic method. Nevertheless, the onset of papilloedema in any variety of hypertension is of ominous significance. At the moment we have a patient with severe hypertension who is known to have had papilloedema five years ago, when seen at a large eye hospital in London, and who has had no treatment at all during this period.

The fall in blood pressure continued when patients were put on to the methonium compound, but as soon as they were allowed up the blood-pressure levels began to rise again. This was most noticeable with those receiving pentamethonium bromide. However, hexamethonium bromide orally was no more effective in keeping the blood pressure down in the two patients receiving pentamethonium initially and hexamethonium subsequently (Cases L.M. and E.H., Table VI) in doses in excess of 4 g. daily by mouth.

The initial injection almost invariably produced a fall in blood pressure, and this occurred when the patient was in bed and lying propped up by pillows. This fall was temporary in every case and never exceeded two hours in duration; in many cases it lasted no longer than 20 minutes. In one case the blood pressure fell to zero in less than 15 minutes, though the patient was supine—(Case F.E.: Table III)—the patient becoming unconscious in less than 10 minutes and dying two hours later in spite of injections of adrenaline. Unfortunately, permission for necropsy was not granted, but we felt that a coronary thrombosis was the most likely cause of death.

In every case seen as an out-patient two weeks after discharge the blood pressure, in spite of continuing oral therapy, was as high as it ever was before treatment was begun, even though often the patient was relieved of symptoms. We feel, as stated below, that this symptomatic relief was a bromide effect.

In a few cases in women the 17-ketosteroid excretion after taking the methonium compound was half what it was during the control period. This may possibly be related to the excretion of the bromide ion in the methonium salt. However, in no case was there any suggestive alteration in the excretion of sodium and potassium ions during a period after the institution of the drug when compared with a control period before the drug was administered.

17-Ketosteroid Excretion per 24 Hours

Case:	A	B	C	D	E	F
	mg.	mg.	mg.	mg.	mg.	mg.
Before methonium compound ..	7·2	20·6 10·6	9·1 10·5	11·6	9·3	5·5
After methonium compound ..	5·1 5·8	7·8 25·5*	10·4 5·5	15·1	13·1 11·0	14·1

Further estimations (Cases D, E, and F), and result (*) in Case B, did not confirm our earlier impressions, but we did notice that in Cases D, E, and F there was little response to rest in bed, or the original fall in blood pressure rapidly returned to its previous level.

Whatever the explanation of these figures we felt they were worth while quoting, as they may be related in some way to the metabolism of the bromide ion, or, at the worst, they are of no significance at all.

Complications

All but one of the complications recorded (Case T.H.2) occurred in patients receiving the pentamethonium compound, but most of the bromide levels quoted are from patients receiving hexamethonium bromide.

Two patients (A.L. and H.H.) developed hemiplegia while receiving the drug. It should be noted that in Case H.H. the blood-pressure fall began the day before the drug was started, hemiplegia developed 24 hours after the drug was given, and the slight fall in blood pressure continued while the patient was in hospital and not on the drug, as this was omitted immediately the hemiplegia was noted.

One patient with malignant hypertension who had had a bilateral sympathectomy some 14 months earlier, with no relief of symptoms, became unconscious within 15 minutes after intramuscular injection of 25 mg. of pentamethonium bromide, and died two hours later (Case F.E.). However, a second case in which bilateral sympathectomy had failed responded in exactly the same fashion as did the other cases in this series (Case T.B.), and therefore the fatal result in Case F.E. could not be put down to the use of the drug in a sympathectomized patient, particularly as in both cases operation had completely failed to produce a fall in blood pressure, and in the fatal case had not relieved the patient's symptoms.

A further case (J.W. in Table III, Case 4 in Table I) became drowsy and disorientated two weeks after beginning treatment with pentamethonium bromide. His blood pressure had not fallen to an unduly low level, and during this phase he showed no focal neurological phenomena, nor did he later develop any. The drug was stopped, and after about four days he gradually recovered. This case is comparable in symptomatology and absence of neurological signs to that quoted by Ball (1950). Two weeks after he had returned to his normal mental state, more than four weeks after starting the drug and 19 days after discontinuing it, we found his serum bromide to be 100 mg. per 100 ml. This would indicate that in fact he had been suffering from bromide poisoning. He was receiving 3½ g. of pentamethonium bromide daily—equivalent to about 1½ g. of bromide ion. Since that episode we have taken weekly or fortnightly serum-bromide levels in all our patients, and find that they vary from 25 to 75 mg. per 100 ml. or higher.

Within wide limits, irrespective of the maintenance dose of the drug, the serum-bromide level steadily increased with continuing treatment—e.g., Case L.M. 25 mg., 75 mg., and 80 mg. per 100 ml. of serum at fortnightly intervals; Case A.B. negligible, and 60 mg. and 75 mg. per 100 ml. of serum at approximately three-weekly intervals; and Case E.H. 25 mg., 50 mg., and 60 mg. per 100 ml. of serum at approximately three-weekly intervals. These figures can be repeated for almost every case receiving either hexamethonium or pentamethonium (See Table I). The level increased without corresponding increase of the dosage of methonium compound, and this is almost certainly due to poor excretion of the bromide ion. Further observations will no doubt show a stable serum level balanced at a height proportional to the rate of excretion and the daily dose ingested. The presence or not of toxic symptoms due to this level of bromide ion will then depend upon the height at which this occurs and the patients' susceptibility to the ion.

Some of the patients in this group were receiving a low sodium diet and hence had a low chloride intake. However, the patients with symptoms of bromide intoxication were not on a salt-free diet. In our small series there did not seem to be any close relation between chloride intake and serum-bromide levels. This matter was not investigated in any great detail, though it would seem that a low chloride intake would increase the possibility of a higher serum-bromide level and therefore a greater possibility of bromide intoxication in a susceptible individual. Smirk (1950) found that the drug reduced nervousness and tenseness and that patients were sleepy during the day and the night. He does not mention serum-bromide levels in his communication, but it would seem that these symptoms can reasonably be due to this factor.

It would appear from past experience that the relation between serum-bromide level and symptoms of bromide intoxication is fairly close in all patients receiving continuous bromide treatment. Levels of 50 mg. to 150 mg. per 100 ml. serum correspond to some degree of mental confusion, 150 mg. to 250 mg. to incoordination, and 200 mg. to toxic psychosis. On discontinuing the administration of the bromide the blood level falls slowly at the rate of about half in one month (Wagner and Bunbury, 1930; Gundry, 1939; Sharpe, 1934). It would thus seem that mental phenomena appeared in Case J.W. when his serum-bromide level was about 150 mg. or higher. Incidentally, this patient's serum-bromide level was 75 mg. five weeks after discontinuing all pentamethonium therapy.

Since a single dose of 1 g. or 2 g. of sodium bromide will calm excessive restlessness, quiet pathological excitability, and lessen apprehension, we might well ask whether it is conceivable that the amelioration of symptoms of these patients is due more to the bromide intake than to the methonium compound and not in any way related to the apparent effect of the methonium radical on the autonomic system.

Anorexia was marked in a few cases receiving large oral doses of pentamethonium bromide, and this too may be a bromide ion effect.

It would be of interest to compare these results with a comparable group of patients receiving the chloride or iodide salt. We do not doubt that the acute hypotensive effects would occur, but it is interesting to speculate on what effect the absence of the sedative action of the bromide ion would have on the results. Kay and Smith (1950) in their work have found the chloride less active when given orally. A related drug with a more potent effect, and therefore used in smaller dosage, and containing the bromide ion would give lower serum-bromide levels and make the possibility of bromide intoxication much less likely. It would thus combine the theoretical advantages of the sedative and the hypotensive agent. What is, however, ideally required is a hypotensive agent gradual in onset and much more prolonged in action.

In view of the effect of the drug on ocular accommodation, regular estimates of the intraocular pressure both before and after using the drug were made by

Dr. A. Nazroo. In general the pressure did not change in any particular direction, and therefore if the drug were useful in vascular hypertension it would not necessarily be contraindicated by a raised intraocular tension.

Discussion

Before claiming any clinical value for the methonium compounds in the long-term treatment of hypertension, we feel that a more detailed appreciation of the natural history of essential hypertension would not be quite out of place. Results showing a persistent fall in blood pressure in nephritic patients must take into account the frequent possibility of the subsidence of an acute exacerbation in chronic nephritis. The natural fall in blood pressure in the middle trimester of pregnancy should not be disregarded in hypertensive pregnant patients.

In our series of known hypertensives, some of long standing, rest in bed in many cases produced a fall in blood pressure, occasionally almost to normal levels. The methonium compounds would seem to produce a somewhat greater fall, perhaps because some blood-pressure measurements were made during the period of temporary hypotension each dose provokes, in which case the figures are no exact guide to the true improvement of the patient.

If the drug is only of value in these cases of labile hypertension and produces results no more effective than bed rest, it is in our opinion far too dangerous and troublesome for general use. At the moment there is certainly no indication that it should be used at all outside of hospital. The immediate sharp fall in the blood pressure may be of some value in acute left ventricular failure or hypertensive encephalopathy due to hypertension from any cause, but this has yet to be proved.

As long-term ambulatory treatment for hypertension, the drugs, when given orally for their persistent hypotensive effect, were certainly of no value at all in our series. The necessity for repeatedly increasing the injection dose level, too (Case T.H.), and the gradual return of the average daily blood-pressure level when the patient was up, even in hospital, would suggest that the drug is of doubtful value when given by intramuscular injection in the long-term treatment of hypertension. In Case T.H. there was no immediate fall at all with the intramuscular injection of 50 mg. of hexamethonium bromide. A slight immediate fall of the systolic blood pressure occurred in the first 15 minutes with 75 mg. of the drug, but even this effect ceased to occur after he had received 75 mg. intramuscularly three-hourly for a few days. After ten days of injections and several days of oral therapy he became disorientated, and his blood-bromide level had risen from 15 mg. per 100 ml. of serum six days after starting treatment to 40/100 ml. in 19 days. In yet another case (Case T.H.2) not only was there a failure of the blood pressure to fall, but the mean blood pressure actually rose while he was receiving hexamethonium bromide orally. The dose of hexamethonium bromide was increased to 12 g. daily. At that level his serum bromide was found to be 100 mg. per 100 ml. and he became disorientated. Improvement of his mental condition occurred on stopping the drug, but there was no change in the hypertension. Blurring of his optic disks was visible in the later stages and there was slight albuminuria; and it would therefore seem that the drug could not prevent an acceleration in the progress of his hypertension. Case E.U. has been readmitted to hospital with recurrent attacks of pulmonary oedema while taking 4 g. of hexamethonium daily.

As stated earlier in this paper, many patients admitted to a subjective improvement without any objective evidence for this. It should be recalled that many symptoms in these patients are due to anxiety over the knowledge that they have hypertension rather than directly due to the hypertension, and hypertensives are hyperreactive to anxiety (Hines, 1940). Mental relaxation has always been an effective method of tiding these patients over a crisis, and, for this, phenobarbitone, ½–1 gr. (32–65 mg.) thrice daily, or potassium bromide, 5–10 gr. (0.32–0.65 g.) thrice daily, has been standard (Wood, 1950). The serum-bromide levels with this oral dose of bromide do not approach the levels which we have observed with hexamethonium bromide.

It is of interest to note that Kempner (1949) reported an improvement in 70% of 777 cases treated on the rice diet and, further, that this improvement (improvement in cardiographic pattern, decrease in heart size, disappearance of papilloedema, haemorrhages, and exudates) seemed to bear little relation to the fall in blood pressure, and often occurred on this diet without any decrease in blood pressure.

Watkinson and Evans (1947) reported clinical benefit and an appropriate fall in blood pressure in 60% of patients treated with thiocyanate, but Bechgaard (1946) found that 58% of 1,000 cases of persistent hypertension did well without any treatment whatsoever.

The dramatic write-up which these drugs have received in the daily press, the optimism of the physician using them, the ancillary treatment often used, such as rest in bed, the sedative effect of the bromide ion, are all bound to impress the patient. We would expect anxiety to be relieved and with it some fall in blood pressure and a marked symptomatic improvement in many patients, if only for psychological reasons. We feel that the improvement in our patients is more due to these latter reasons than because of any specific effect of the methonium compounds.

Finally, we would again like to emphasize the fact that these drugs, by injection, do produce an acute fall in blood pressure, and this acute fall may exceed 200 mm. Hg; but this effect does not last, and other hypotensive agents—e.g. tetraethylammonium chloride—can be no less effective in this respect. We do not feel that the therapeutic value of these drugs in the long-term treatment of hypertension should be assessed by their known ability to produce an acute fall in blood pressure.

The drug is certainly not harmless, and, even were the several acute cerebral catastrophes of no statistical importance, the high blood-bromide levels and the cases of bromide intoxication would indicate the advantage of using a less toxic ion, even if methonium compounds were of value.

Summary

A trial of pentamethonium and hexamethonium bromide was instituted in 34 cases of persistent hypertension.

Before starting the use of the drug each patient was given two weeks' initial observation, routine treatment, and rest in bed. This period was used to control the final results.

In every case the methonium compounds were hardly any more effective in lowering blood pressure than the bed rest period.

Observation of these cases as out-patients showed a complete failure of the drugs to lower or maintain a low blood

pressure when given orally. One death probably attributable to the drug is reported, and also three probable cases of bromide intoxication.

Reasons are given for believing that the sedative effect of the bromide ion, aided by ancillary factors, was one of the main agents in the subjective improvement in these patients.

We are grateful to our ward sisters, without whose co-operation this work could not have been done; to Dr. J. Lister and Dr. J. Angus for their unfailing help in the treatment of these cases; and to Mr. D. G. Nutt for his skilled biochemical assistance. We also wish to thank Messrs. May and Baker Ltd. for the adequate supply of the drugs necessary to conduct this trial, and Mrs. E. D. Price for her skilled secretarial help in writing this paper.

ADDENDUM.—Since the above was written we have used the drug in a further 12 cases, with results exactly as before. Only one patient showed any response to oral therapy as an out-patient. On 4 g. of hexamethonium bromide daily her blood pressure fell from 260/140 to 120–140/70–95, and she complained of persistent dizziness and vertigo. Her serum-bromide level was 35 mg. per 100 ml. Intramuscular ephedrine—½ gr. (32 mg.) given on four occasions—did not result in an elevation of blood pressure. Without the hexamethonium bromide her blood pressure kept at this level for 48 hours, and then slowly climbed to its previous height with relief of all her symptoms. She had no desire to continue taking the drug.

We note that two cases of bromide poisoning (Rosenheim, 1951; Holt, 1951) have now been reported. We are also investigating the value of the drug when given subcutaneously as recommended by Smirk (1950).

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Because bats are nocturnal creatures and sleep by day in caves, their habits remain something of a mystery. Members of the Devon Speleological Society are now studying individual bats which have received a numbered aluminium ring on the forearm to permit subsequent recognition, and find (*Nature*, April 7, p. 555) that the greater horseshoe bats of South Devon change their sleeping quarters at least weekly, even in midwinter, flying fifteen or more miles in the process. Sometimes the bats sleep alone, sometimes in clusters of anything from six to three hundred individuals, aggregated without distinction of sex. They do not move around with fellow-members of any given cluster but retain their single independence.

ACUTE LEUKAEMIA TREATED WITH A-METHOPTERIN

BY

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The use of folic acid antagonists in acute leukaemia arises from the observation that the administration of pteroylglutamic acid or its conjugates apparently intensifies the leukaemic process (Farber *et al.*, 1947; Heinle and Welch, 1948). The use of synthetic anti-folic-acid compounds was therefore applied in the treatment of acute leukaemia. Several of these compounds are available, all of which, though structurally related to folic acid, are biologically antagonistic (Smith *et al.*, 1948). Meyer (1948) treated five cases of acute leukaemia with the folic acid antagonists pteroylaspartic acid and methylpteroic acid, and obtained temporary clinical and haematological remissions in four; and Farber and his colleagues (1948) reported significant remissions in 10 out of 16 children treated with 4-aminopteroylglutamic acid (" aminopterin ").

In a later report, Farber (1949) summarized data on 60 children with acute leukaemia treated with aminopterin, 4-amino-N10-methylpteroylglutamic acid (" a-methopterin "), and 4-aminopteroylaspartic acid (" amino-an-fol "). Clinical and haematological remissions were obtained in 50% of these patients, and in two cases were maintained for 16 and 23 months. The reported incidence of remissions in cases treated by other authors varies from 9% (Meyer *et al.*, 1949) to 45% (Pierce and Alt, 1948). Dacie *et al.* (1950), in a study of 13 cases treated with aminopterin, found that remissions were induced in nine. Seven of these patients were children, and all showed a significant response of varying duration, the maximum period of survival being nine months. Only two of the six adults had partial remissions lasting four to six weeks. The lymphoblastic type of leukaemia appeared to be most responsive.

In this paper we report the results of treatment with a-methopterin in seven cases of acute leukaemia. It was hoped that this antagonist might prove less toxic than aminopterin yet as efficacious in inducing remissions, but the results obtained have been largely disappointing in this respect.

Case 1. Acute Myeloblastic Leukaemia

A housewife aged 35 was transferred from another hospital on October 17, 1949, for treatment with folic acid antagonists. She had been admitted there on October 8 with a two months' history of increasingly severe palpitations, shortness of breath, menorrhagia, and loss of weight. Examination disclosed severe anaemia, enlargement of the spleen and liver, and a leucocytosis of 28,000 per c.mm., some 93% of the cells being leukaemic blast cells. She was transfused with a litre of blood before being sent to Hammersmith Hospital.

On admission the patient was well nourished but pale. Her temperature was 100.2° F. (37.9° C.). Her skin and throat appeared healthy. Only one small lymph node was

palpable, in the right submandibular group. Her spleen was felt 4 cm. and her liver 10 cm. below the costal margin, and her left kidney was palpable. No other abnormalities were found on clinical examination, and examination of the urine was negative. A chest radiograph was normal.

A blood count showed: red cells, 2,600,000 per c.mm.; Hb, 8.9 g. per 100 ml.; reticulocytes, 2.1%; platelets, 130,000 per c.mm.; white cells, 69,000 per c.mm. (myeloblasts 96%, polymorphs 1.5%, lymphocytes 2.5%). There were 10 normoblasts per 100 leucocytes.

On sternal puncture the bone marrow was very cellular and characteristic of myeloblastic leukaemia, the cells being predominantly myeloblasts. Mature granulocytes were few. Erythropoiesis was reduced but normoblastic in type.

Progress and Treatment

Procaine penicillin, 600,000 units daily, was given throughout the illness. Treatment with folic acid antagonists was begun on October 22, 1 mg. of aminopterin being given by mouth for three days. On October 25, when the white cells had risen to 95,000, a-methopterin was substituted, and was given on most days in doses of 5 mg. intramuscularly until November 18; the total amount given was 160 mg. A transfusion of packed red cells from 2 litres of blood was found necessary on the seventh day of treatment because

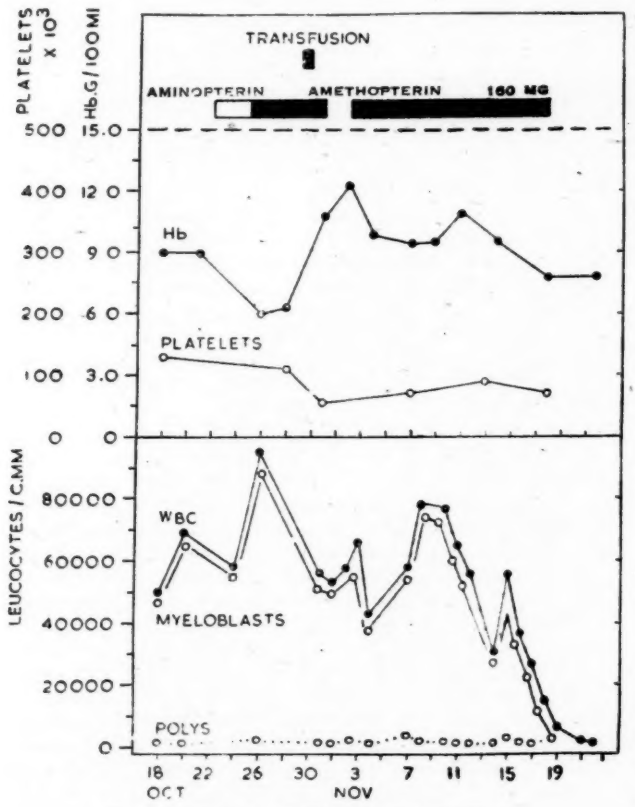

FIG. 1.—Case 1. Treatment and progress.

of a fall in the haemoglobin to 6.2 g. (Fig. 1). On November 9, after 70 mg. of a-methopterin had been given, there was no great clinical change in the patient's condition, although the spleen and liver appeared to be slightly reduced in size. Her white cell count was 77,000 per c.mm., of which 99% were myeloblasts. Reticulocytes were low (1%) and the platelets had fallen to 68,000 per c.mm. Sternal puncture showed no change in the bone marrow.

After 120 mg. of the drug had been given, the patient complained of a little dysphagia, but there were no abnormal physical signs and the leucocyte count was still 56,000 per c.mm. Her mouth and throat remained clear and there was no overt bleeding. From then onwards the white cell count fell gradually, and on November 18 treatment was discontinued. The leucocyte count was 15,000 per c.mm., but 99% of the cells were still myeloblasts. The sternal marrow at this stage showed reduced cellularity but no increase in maturity of the granulocytes. Clinically, the patient remained unchanged; dysphagia had almost disappeared and there was no significant alteration in the size of the spleen or liver. She remained febrile, and her haemoglobin had fallen to 7.2 g. since the previous transfusion.

Three days after the discontinuation of treatment her temperature rose abruptly to 104° F. (40° C.), and she suddenly developed deafness in the left ear. Her leucocyte count fell to 1,800 per c.mm. Physical examination revealed a left middle-ear type of deafness and signs of bronchopneumonia at both lung bases. Her throat appeared normal. On the following day, November 22, she developed hyperpyrexia and hyperpnoea and died.

Necropsy Findings

Necropsy (Dr. A. J. M. Reese) revealed a few petechial haemorrhages on both arms. Both lungs were oedematous, with exudation of protein-rich fluid into the alveoli, but without leucocytic infiltration. The mouth, pharynx, and upper oesophagus were normal, but the lower two-thirds of the oesophagus was oedematous and the hyperaemic mucosa was covered with ulcers, confluent in places, which formed longitudinal areas of ulceration with black, sloughing bases and raised red margins. Three similar ulcers were present in the stomach and six were scattered throughout the ileum. The remainder of the intestinal tract was normal. Histologically, these ulcerated areas showed an absence of cellular infiltrations, although there was oedema of the submucosa and slight perivascular infiltration of leukaemic cells in the adjacent mucosa. The liver and spleen revealed nothing remarkable to the naked eye, but on section both organs showed a moderate degree of myeloblastic infiltration.

The kidneys were not enlarged and appeared normal macroscopically, but section demonstrated a little subcapsular leukaemic infiltration. The lymph nodes generally were uniformly infiltrated with primitive cells. The bone marrow of the sternum, vertebral bodies, and femur was red and rather pale, and in the centre of the femur it was gelatinous. Microscopically, it was uniformly cellular, and that from the femoral diaphysis was oedematous. Most of the cells were primitive. Giant cells with two to five nuclei were frequent, as were mitotic figures. Normoblastic erythropoiesis was present, though diminished.

The remainder of the organs were macroscopically and microscopically normal, apart from the demonstration of haemorrhage into the left middle-ear cavity.

Comment.—A course of 3 mg. of aminopterin and 160 mg. of a-methopterin produced a gradual reduction in the leucocyte counts in a case of myeloblastic leukaemia. Treatment was discontinued when the leucocyte count had fallen from 69,000 to 15,000 per c.mm., but the count fell to leucopenic levels after the drug was stopped, and bleeding occurred into the left middle ear. Death occurred four days afterwards. At necropsy there was leukaemic infiltration of viscera, lymph nodes, and bone marrow. Ulceration of the oesophagus, stomach, and ileum was present and was associated with leukaemic infiltration.

Case 2. Acute Lymphoblastic Leukaemia

A girl aged 2 was well until five weeks before admission, when she was noted to be pale and fretful and to have lost her appetite. Two weeks later she became feverish and developed petechial haemorrhages on the limbs and trunk. The child was admitted to another hospital on October 11, 1949, for investigation. She was found to have lymphoblastic leukaemia, and after a transfusion of 560 ml.

of blood was sent to Hammersmith Hospital on October 21 for further treatment.

On admission the child was very ill and looked pale and sallow. Her temperature was 104° F. (40° C.). Petechial haemorrhages were present in the skin over the trunk and limbs and in the mucosa of the palate, and there was a recent bruise above the right eye. Her gums were swollen and friable, and her pharynx was injected. All superficial lymph nodes were greatly enlarged. The liver was palpable at the level of the umbilicus, and the spleen, which was firm and tender, extended down into the left iliac fossa. The heart, lungs, and nervous system were clinically normal, and no abnormality was noted in radiographs of the chest and long bones.

A blood count showed: red cells, 2,200,000 per c.mm.; Hb, 6.4 g. per 100 ml.; reticulocytes, 0.4%; platelets, 36,000 per c.mm.; white cells, 13,000 per c.mm. (blast cells 4%, segmented polymorphs 12%, large and small lymphocytes 83%, monocytes 1%).

Bone marrow was obtained by tibial puncture. Most of the cells present were of the lymphocyte series, about half being lymphoblasts. Erythropoiesis and granulopoiesis were minimal. Megakaryocytes were very scanty. The appearance was of an acute lymphoblastic leukaemia.

Progress and Treatment

The cells of 1 litre of blood were given by transfusion on the day after admission, and a-methopterin, in doses of 2.5 mg. by mouth daily, was begun on October 24; five doses, totalling 12.5 mg., were given. In spite of the transfusion there was no improvement in the patient's condition. Purpura became widespread, and an incision over the right ankle, made for the purpose of transfusion, bled freely and remained unhealed. Her temperature was still high. She died on October 29, eight days after admission. On the day of death her leucocyte count was 1,000 per c.mm., 64% of the cells being lymphocytes and the remainder polymorphs.

Smears of the tibial bone marrow made immediately after death showed 60% of the cells to be of the lymphocyte series, about a third of them lymphoblasts. Compared with the pretreatment biopsy, developing granulocytes were quite numerous, and there were some erythroblasts; haemopoiesis appeared to be more normal.

Necropsy Findings

The post-mortem examination was carried out by Dr. B. Lennox. The trunk, limbs, and buccal mucosa were covered with petechial haemorrhages, and there was an unhealed cut-down wound over the right ankle. Internally, petechiae were widespread on the serous surfaces of the heart, lungs, and abdominal viscera, and in the mucosa of the stomach and small intestine. Scattered small haemorrhages were present beneath the meninges and in the cortical grey matter of the brain. All the lymph nodes were moderately enlarged, and their architecture was replaced by a uniform infiltration with lymphocytes. The thymus also was densely infiltrated with leukaemic cells. The liver was moderately enlarged and its cut surface presented scattered white nodules. Microscopically, these consisted of areas of lymphocytic infiltration. The spleen was greatly enlarged and its pulp replaced by leukaemic tissue. The kidneys showed subcapsular haemorrhages and patchy interstitial leukaemic infiltrations. The bone marrow of the sternum, long bones, and vertebrae was deep red and gelatinous. Microscopically its structure was as seen in the post-mortem aspiration.

Comment.—In this case of lymphoblastic leukaemia in a child of 2 years with a very short history death occurred from haemorrhagic complications after 12.5 mg. of a-methopterin had been given. The marrow appeared to be responding by increased granulopoiesis and erythropoiesis, as judged by the final blood count and by the appearance of the bone marrow after death as compared with that before treatment. The course of the illness after admission was too short to assess the effects of treatment on liver, spleen, and lymph-node enlargement.

Case 3. Subacute Myeloblastic Leukaemia

A boy aged 15 was admitted on November 1, 1949, with a history of increasing fatigue, joint stiffness, and breathlessness on exertion of four weeks' duration. On admission he was found to be gravely anaemic with signs of right-heart failure. His superficial lymph nodes, liver, and spleen were all palpable and moderately enlarged. There were no other abnormalities on physical examination, and a radiograph of the chest was normal.

His blood count was as follows: red cells, 630,000 per c.mm.; Hb, 3.4 g. per 100 ml.; platelets, 45,000 per c.mm.; white cells, 178,000 per c.mm. (blast cells 17%, promyelocytes 5%, myelocytes 13%, metamyelocytes 19%, polymorphs 39%, lymphocytes 7%).

Sternal puncture revealed a highly cellular marrow with numerous peroxidase-negative myeloblasts and promyelocytes, but there was also a good deal of differentiation to adult granulopoiesis, indicating a subacute type of myeloblastic leukaemia. Erythropoiesis was scanty but of normoblastic type. Few megakaryocytes were present.

Progress and Treatment

The patient was transfused during his first week in hospital. In view of the subacute nature of the leukaemia and the high initial leucocyte count, it was felt that deep *x*-ray therapy offered the best chance of successful treatment. Accordingly, he was treated by generalized body irradiation for one month. During the early stages of treatment he developed arthralgia and painful effusions in his finger-joints and left knee and ankle. There were no radiographic changes and the symptoms subsided completely in 10 days. After the course of irradiation was completed his liver and spleen were no longer palpable and his peripheral leucocyte count was reduced to 63,000 per c.mm. There was, however, no change in the distribution of leucocytes, and the appearance of the sternal bone marrow was unaltered. The haemoglobin and red cell counts fell consistently during treatment, and further blood transfusions were required.

Three weeks after irradiation the leucocyte count had risen to 200,000 per c.mm., most of the cells being immature granulocytes. His liver, spleen, and lymph nodes were once more palpable, and he had developed a purpuric rash. He complained of pains in both hands, feet, and elbows, and had effusions in his metacarpo-phalangeal joints. Radiographs showed periostitis of the right fibula and the third right metacarpal. Treatment with a-methopterin was begun on December 30, 2.5 mg. being given daily by mouth. The drug was discontinued on the eleventh day, after 27.5 mg. had been given, because of the sudden development of bilateral middle-ear deafness. The total and differential white cell counts in the blood were unchanged, but the liver and spleen were smaller and the joint effusions had absorbed rapidly after treatment had begun. Next day the patient became comatose and died of an intracerebral haemorrhage.

Necropsy Findings

Post-mortem examination (Dr. I. Doniach) revealed scattered petechial haemorrhages on the limbs and trunk. The cause of death was a massive intracerebral haemorrhage, and bleeding had occurred into both middle-ear clefts. The pericardial surface of the heart and the gastric mucosa were covered with petechial haemorrhages. The liver, spleen, and lymph nodes generally were all greatly enlarged and firm. The sternum and long bones were filled with bright red marrow. The rest of the viscera, endocrine glands, and alimentary tract appeared normal. Histologically, the small vessels throughout the body contained many white cells, and there was widespread infiltration of the tissues by leukaemic cells. The pericardium, heart, lungs, stomach,

liver, kidneys, spleen, lymph nodes, and testes all showed varying degrees of infiltration, which involved also the synovial membrane and periosteum of the right knee, right third metacarpo-phalangeal joint, and right ankle. Bone marrow from the sternum and long bones showed intensive and uniform proliferation of primitive leukaemic cells.

Comment.—This case of subacute myeloblastic leukaemia showed only a very transient and partial response to deep *x*-ray therapy. A course of a-methopterin was discontinued after 27.5 mg. had been given, because of haemorrhage into both middle ears, and this was immediately followed by a fatal cerebral haemorrhage. At necropsy all organs were heavily infiltrated with leukaemic cells and the bone marrow was hyperplastic and leukaemic.

Case 4. Myeloblastic Leukaemia

A schoolboy aged 14 had acute appendicitis in January, 1949. At operation it was noted that there were many calcified lymph nodes in the mesentery and one that was acutely inflamed and suppurating. The boy recovered from the operation and appeared to be well until October, 1949, when he was abnormally pale and tired easily. These symptoms increased, and by the end of November he was confined to bed with general weakness, anorexia, dyspnoea on exertion, and fever. He was admitted to hospital on December 6 for investigation.

On admission the boy was well nourished but very anaemic. His temperature was 104° F. (40° C.). His skin, throat, and mouth appeared to be healthy. Lymph nodes in the cervical, axillary, and inguinal groups were moderately enlarged and firm. His liver was enlarged 4 cm. and his spleen to 1 cm. below the costal margins. No other abnormality was found on physical examination, and radiographs of the chest and long bones were normal.

A blood count showed: red cells, 1,900,000 per c.mm.; Hb, 7.3 g. per 100 ml.; reticulocytes, 1.3%; platelets, 50,000 per c.mm.; white cells, 67,000 per c.mm. (blast cells 90%, polymorphs 1%, lymphocytes 7.5%, monocytes 1.5%); nucleated erythrocytes, 2 per 100 white cells.

Sternal puncture revealed a highly cellular marrow, most of the cells being myeloblasts. Granulocyte and erythrocyte development was scanty.

Progress and Treatment

From the time of admission the patient had a remittent temperature rising to 104° F. (40° C.) and accompanied by rigors and sweating. On his third day in hospital he was transfused with packed red cells from 2 litres of blood, and on that day and the next he was given 5 mg. of a-methopterin by intramuscular injection. Shortly after the second injection he developed central abdominal pain and vomiting, and these symptoms increased during the succeeding days. Penicillin was administered parenterally, but his condition deteriorated progressively. He became drowsy and slightly icteric, and bled from the nose and gums. Petechial skin haemorrhages developed and fundal haemorrhages were noted. A further blood transfusion was given on December 14, but a few hours afterwards he became completely unconscious and died the same night, nine days after admission.

Although only 10 mg. of a-methopterin had been given there was a profound effect on the white cells, which fell from 65,000 per c.mm. on the day the first injection was given to 1,600 per c.mm. two days later and 200 per c.mm. on the day of death. Blast cells disappeared and were replaced by mature granulocytes and lymphocytes in equal proportions. The haemoglobin level fell rapidly after the first transfusion, and there were few platelets in the blood at any time.

Necropsy Findings

Post-mortem examination (Dr. C. V. Harrison) showed that the body was moderately jaundiced with a petechial cutaneous rash. Petechial haemorrhages were also present under the pericardium and in the mucosa of the stomach and intestine. There was a haemorrhage into the lower lobe of the left lung. The lymph nodes generally were enlarged and fleshy except for those in the mesentery, which were calcified. Histologically they showed a sinus and medullary reaction and contained many foci of primitive cells. The mesenteric glands showed healed tuberculosis. The liver was enlarged, and on section contained many small ramifying abscesses with necrotic centres. They contained colonies of cocci with virtually no surrounding cellular reaction. There was no evidence of leukaemic infiltration.

The spleen was enlarged; in its pulp were clusters of marrow cells, many of them primitive myeloblasts. The long bones, sternum, and vertebrae were filled throughout with red marrow, with, microscopically, an almost complete absence of recognizable cells. Odd foci of leukaemic cells, mostly myeloblasts, were present, and large phagocytic macrophages were scattered throughout. The appearances suggested almost total destruction of the marrow, of recent origin. The kidneys were normal, and no abnormality was found in the remaining organs.

Cultures taken post mortem from the liver abscesses grew a penicillin-resistant *Staph. aureus*. Acid-fast bacilli were not found, and culture for *Myco. tuberculosis* was negative.

Comment.—Myeloblastic leukaemia in a boy, occurring eight or nine months after an attack of acute appendicitis, was complicated by jaundice and abdominal symptoms: 10 mg. of a-methopterin rendered the bone marrow aplastic. At necropsy a staphylococcal portal pyaemia was found, presumably related to the previous appendicitis.

Case 5. Paramyeloblastic Leukaemia

A housewife aged 32 had a three-months history of increasing fatigue, lassitude, palpitations, and headaches. For six weeks she had observed swelling of the hands and finger-joints, and for two weeks had breathlessness on exertion and a tendency to spontaneous bruising of the limbs and trunk. Increasing pallor had been noted for the same period. She was feverish, and had night sweats for a week before admission to hospital on January 4, 1950.

On admission the patient was in right-sided heart failure due to severe anaemia. She had a few old bruises on the legs and arms. Her superficial lymph nodes were all enlarged, and her liver and spleen were palpable 5 cm. below the costal margins. No abnormality was noted in the hands or other joints, and radiographs of the chest and hands were normal.

Her blood count was as follows: red cells, 900,000 per c.mm.; Hb, 3.8 g. per 100 ml.; reticulocytes, 1.5%; platelets, 11,000 per c.mm.; white cells, 42,000 per c.mm. (blast cells 54%, metamyelocytes 8%, polymorphs 18%, basophils 1%, lymphocytes 7%, abnormal monocytes 12%); nucleated erythrocytes 3 per 100 white cells.

On sternal puncture the bone marrow showed a predominance of primitive blast cells having the appearance of aberrant myeloblasts. They differentiated both to granulocytes and to abnormal monocyte-like cells. Mature granulocytes were few, and the scanty erythroblasts present were partially megaloblastiform in type. The appearance was of a paramyeloblastic leukaemia (Naegeli type "monocytic" leukaemia).

Progress and Treatment

The patient was given parenteral penicillin daily whilst in hospital, and during the first week small transfusions of packed red cells to bring her haemoglobin to 12.9 g.

Treatment with a-methopterin was begun on January 10. 5 mg. being given on most days by mouth. On January 29 the dose was increased to 10 mg., and treatment was discontinued on February 9 after 180 mg. had been given. For the first three weeks of treatment the patient's general

condition was fairly good, and she remained afebrile. She did, however, have an increased tendency to bleed, and for a few days had impaired vision due to bilateral fundal haemorrhages.

During the last three days of treatment she developed slight pyrexia, sore throat, and superficial ulceration of the lips, throat, and fauces, symptoms which subsided three days after cessation of therapy. The results were disappointing. There was a slight diminution in the size of the enlarged liver, spleen, and lymph nodes, and the peripheral white cell count was reduced to 6,000 per c.mm. (Fig. 2), but there was no significant change in the distribution of leucocytes in either the blood or the bone marrow, and the platelet and reticulocyte counts remained low. A steady fall in the patient's haemoglobin level necessitated a further transfusion on February 11, and she was discharged on February 13. Whilst at home she was instructed to take 1 mg. of aminopterin by mouth three times weekly.

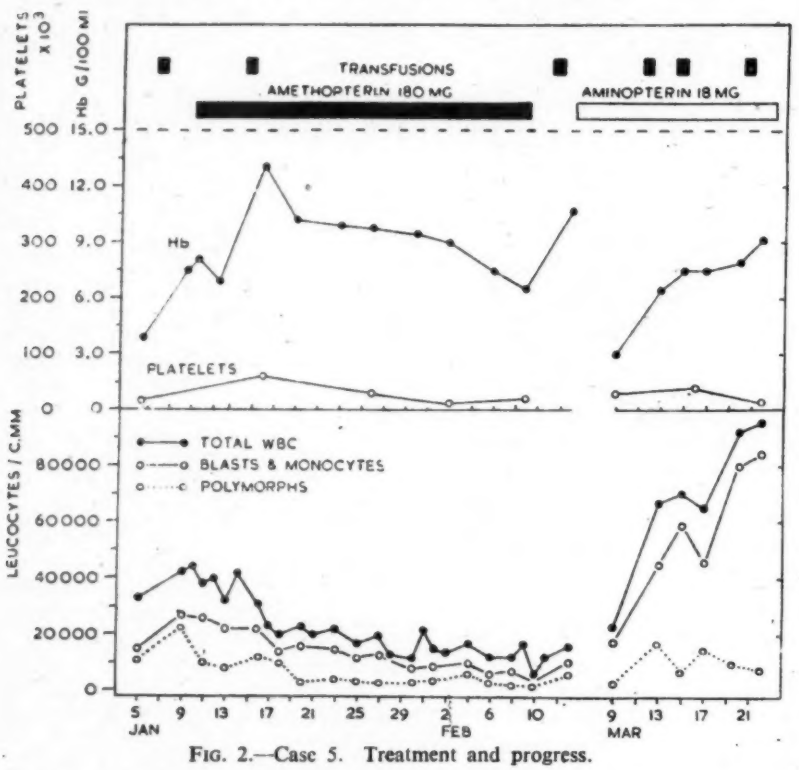

FIG. 2.—Case 5. Treatment and progress.

Three weeks later the patient was readmitted, greatly exsanguinated, following a severe rectal haemorrhage. She had also developed generalized purpura and bleeding from the gums, and enlargement of the spleen, liver, and lymph nodes had increased. Her peripheral white cell count had risen to 30,000 per c.mm., of which 68% were myeloblasts or paramyeloblasts and 15% were abnormal monocytes. Two more transfusions of packed red cells were given, and treatment with aminopterin was continued in the same dosage—1 mg. thrice weekly. Although there was no recurrence of the rectal haemorrhages which had led to her admission, the patient had a constant tendency to bleed from the gums and into the skin, and this prevented any increase in the dose of the folic acid antagonist. The patient was discharged again on March 23, symptomatically improved, but with a still rising white cell count. She died at home a month later, after a short period of coma. The apparent cause of death was intracerebral haemorrhage. Permission for a necropsy was not obtained. The total amount of aminopterin given was 18 mg.

Comment.—The leukaemia in this case was of the paramyeloblastic type. A course of 180 mg. of a-methopterin, sufficient to produce symptoms of toxicity, caused a transient lowering of the peripheral white cell count and slight objective clinical improvement, but had no effect on the differential white cell count in the blood or bone marrow. Haemorrhagic complications were severe. Further treatment with aminopterin, 1 mg. thrice weekly, the maximum dose tolerated, was ineffective in halting the course of the disease, and death ensued from cerebral haemorrhage.

Case 6. Lymphoblastic Leukaemia

A girl aged 8 was admitted from another hospital for treatment of lymphoblastic leukaemia. Her history dated from the middle of October, 1949, when she had a feverish illness, accompanied by headache, abdominal pain, and vomiting, which was diagnosed as influenza. The fever subsided in 14 days, but the child remained irritable, anorexic, and fretful, and enlarged glands were observed in her neck. Towards the end of November she developed, in addition, pains in the limbs. Investigation at another hospital during December revealed a moderate degree of anaemia, generalized lymphadenopathy, and enlargement of the liver and spleen. Examination of the blood showed an acute leukaemia, so she was transferred for treatment with folic acid antagonists on January 5, 1950.

On admission the child was well nourished and appeared only mildly anaemic. Her temperature was 101.4° F. (38.55° C.). Her skin, throat, and mouth appeared healthy. All superficial lymph nodes were considerably enlarged, and her left kidney was palpable. The spleen and liver were felt 2 cm. below the costal margins. No abnormality was found in the other systems, and radiographs of her chest, skull, spine, and long bones were negative.

Blood findings were as follows: red cells, 4,200,000 per c.mm.; Hb, 11.2 g. per 100 ml.; reticulocytes, 1.6%; platelets, 12,000 per c.mm.; white cells, 52,000 per c.mm. (blast cells 52%, polymorphs 2%, lymphocytes 46%).

On sternal puncture the normal bone marrow cells were seen to be almost entirely replaced by primitive cells with the characteristics of lymphoblasts. A small percentage of the cells present were adult lymphocytes, but there was little granulopoiesis or erythropoiesis.

Progress and Treatment

The child bled severely from a loose tooth during her first week in hospital, haemorrhage being arrested only after the tooth had been extracted and a litre of fresh blood had been transfused. On January 23 the white cell count had risen to 98,000 per c.mm. Treatment with a-methopterin was begun on that day, and 2.5 mg. of the drug was given by mouth daily for nine days, a total of 22.5 mg. During the first three days of treatment the child had migratory joint pains, but these ceased after four doses of a-methopterin had been given, and did not recur. The only radiographic change was the development of periostitis of the upper end of the left fibula; a radiograph taken three weeks later showed this to have resolved.

Severe toxic manifestations resulted from the administration of a-methopterin, and her general condition deteriorated considerably. She bled from the gums and developed widespread cutaneous and mucosal petechial haemorrhages and haematuria. She also vomited repeatedly. The enlarged lymph nodes, spleen, and liver, however, regressed considerably in size, and the left kidney became impalpable. A further blood transfusion was given on February 18, and

shortly afterwards the child began to recover. She ceased to bleed, her appetite returned, and she regained weight. By February 28 she was considerably improved and fit for discharge home. There was then no palpable enlargement of lymph nodes or viscera, and the child was walking and alert. Instructions were given for her to receive 2.5 mg. of a-methopterin by mouth thrice weekly whilst at home.

The effect of a-methopterin on the blood was to induce a leucopenia, the white cells falling for six days after the drug was withdrawn (Fig. 3). The lowest count, on February 7, was 650 per c.mm., 70% of the cells being lymphocytes and 30% polymorphs. At this stage the bone marrow was hypoplastic. Very few lymphoblasts, comprising only 1% of the marrow cells, were seen; 10% of the cells were lymphocytes, and the remainder were developing granulocytes and normoblasts in equal proportions. Three weeks later, at the time the child was discharged from hospital, the peripheral leucocyte count had risen to 7,000 per c.mm., with a normal distribution of leucocytes.

Two weeks after discharge she was seen again and had clearly relapsed. She was once more anaemic, and complained of pain in the abdomen and joints, vomiting, and epistaxis. Her lymph nodes, spleen, and liver were again greatly enlarged, and her left wrist and right knee were tender and their movements restricted. There were radiographic bone changes in the knees and left wrist. The white cell count had risen to 21,000 per c.mm.; 83% of the cells were blast cells and only 3% were polymorphs. Readmission was advised but was declined, and a-methopterin was continued at home in a dosage of 2.5 mg. on alternate days. The patient died at home 12 days later. Permission for a necropsy was not obtained.

Comment.—A girl with acute lymphoblastic leukaemia and a high initial white cell count was given 22.5 mg. of a-methopterin in nine days. Toxic complications, which included bone marrow damage, were severe, but joint symptoms subsided and visceral enlargement regressed, and there was a coincident improvement in her general condition. The bone marrow and peripheral blood became much more normal in appearance. The clinical and haematological remission lasted less than four weeks. Relapse was not prevented by "maintenance" doses of a-methopterin, and death occurred within a month of discharge from hospital.

Case 7. Acute Lymphoblastic Leukaemia

A boy of 3½ years was admitted from another hospital as a case of lymphoblastic leukaemia for anti-folic-acid therapy. In February, 1950, the child had first been noted to be unduly pallid and was treated by his general practitioner for anaemia. There was no response to treatment, and during April he developed a haemorrhagic lesion in the pulp of the right index finger and a little bleeding from the mouth. He was admitted to another hospital, where a diagnosis of leukaemia was made, and on April 28 he was transferred to Hammersmith Hospital.

Although well nourished and not distressed, the child on admission was very anaemic. There were a few scattered bruises on his legs, and the terminal pulp space of the right index finger was swollen and discoloured by a haemorrhage into it. His throat appeared normal. One enlarged lymph node was palpable in the left axilla, but none elsewhere. The liver and spleen were just palpable under the costal margins. There were no other abnormalities on physical examination, and radiographs of the chest and long bones were normal.

A blood count showed: red cells, 2,400,000 per c.mm.; Hb, 5.8 g. per 100 ml.; reticulocytes, 0.2%; platelets, 10,000 per c.mm.; white cells, 31,000 per c.mm. (blast cells 78%, polymorphs 1%, lymphocytes 21%).

Bone marrow obtained by sternal puncture was highly cellular, about 90% of the cells being nucleolated blast cells and the remainder more or less mature lymphocytes. There was little evidence of either granulopoiesis or erythropoiesis, and no megakaryocytes were seen. The appearance was of an acute lymphoblastic leukaemia.

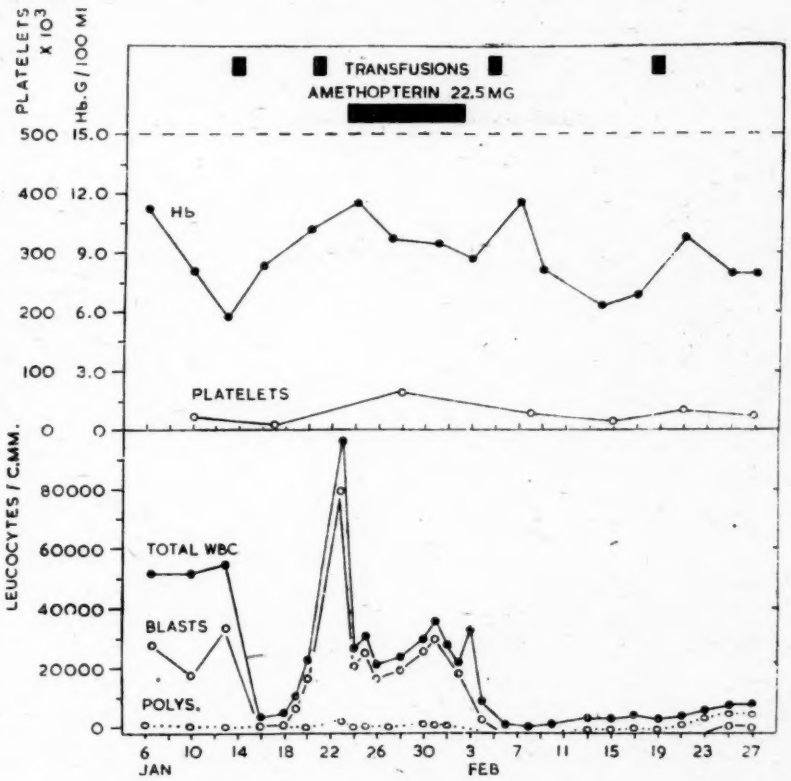

FIG. 3.—Case 6. Treatment and progress.

Progress and Treatment

A blood transfusion given on the day after admission elevated the child's haemoglobin to 11.4 g. Seven daily doses of a-methopterin, each of 5 mg. by mouth, were given between May 2 and 10—a total of 35 mg. in nine days. On the day after treatment was begun he suddenly developed intense dyspnoea and inspiratory stridor and bled from the haematoma in the right index finger and from the rectum. The respiratory symptoms appeared to be associated with a haemorrhage into the left lung and did not completely disappear throughout the illness. During the next week the child developed a high remittent evening temperature, uninfluenced by daily penicillin injection. He also developed petechial haemorrhages into the skin and buccal mucosa, and haematomata formed in the lower lip and in both right eyelids. Rutin given by mouth had no apparent effect on the bleeding. The haemoglobin level fell rapidly, and another blood transfusion was required on May 15. This appeared to have no effect on the course of the illness, and the child's condition deteriorated rapidly. On May 18 he became comatose and died. The immediate cause of death appeared to be a cerebral haemorrhage.

The effect of a-methopterin on the blood was to induce a leucopenia, maximal five days after discontinuing treatment.

The lowest white cell count was 1,400 per c.mm. on May 15; two days later it had risen to 2,500 per c.mm. Leukaemic blast cells disappeared from the peripheral blood; lymphocytes, mostly young forms with clear cytoplasm, constituted 85% of the leucocytes, the remainder being polymorphs and stab cells. Platelets were virtually absent from the blood during the illness. Owing to the child's critical state marrow biopsy was not repeated after admission.

Necropsy Findings

The post-mortem examination was carried out by Dr. I. Doniach. The body was covered with petechial cutaneous haemorrhages, and the right upper and lower eyelids were enlarged by haemorrhage. Internally, petechiae were widespread over the visceral peritoneum, the pleural, epicardial, and endocardial surfaces of the heart, and in the mucosa of almost the whole length of the alimentary tract. The stomach was filled with blood clot, and there was a massive haemorrhage into the left lung. The immediate cause of death was an extensive subarachnoid haemorrhage. The kidneys showed numerous parenchymal haemorrhages on section, and the mucosa of the renal pelvis and bladder was haemorrhagic. The liver and spleen were not enlarged and appeared normal macroscopically. The lymph nodes generally were slightly enlarged and congested. The bone marrow of the sternum, vertebrae, and long bones was plum-coloured and deeply haemorrhagic.

Histologically, there was a notable absence of leukaemic infiltration in any organ, the only abnormality being congestion and haemorrhages. The left lung showed haemorrhagic consolidation and an acute necrosing bronchiolitis. Details of the bone marrow were largely obscured by haemorrhage, but one relatively intact area in the sternum showed large numbers of lymphocytes and normoblasts and a few blast cells, but there was little evidence of active granulopoiesis.

Comment.—A short course of a-methopterin effectively reduced the peripheral white cell count in this case of acute lymphoblastic leukaemia and produced some improvement in the appearance of the blood. Haemorrhagic complications were exacerbated by the drug to an alarming degree and ultimately proved fatal. At necropsy there was a remarkable absence of visceral leukaemic infiltration, the only significant lesions being those due to haemorrhage.

Results

Five of the patients treated were children, of whom three had acute lymphoblastic leukaemia and two had myeloblastic leukaemia. Of the two adults, one had acute myeloblastic leukaemia and the other had paramyeloblastic leukaemia.

The results obtained were, to say the least, disappointing. In only one patient (Case 6) did there appear to be any beneficial response to treatment. This was a case of lymphoblastic leukaemia, clinically acute, and the administration of 22.5 mg. of a-methopterin caused regression of visceral enlargement and an improvement in the child's general condition. Concurrently there was a significant improvement in the state of the peripheral blood and bone marrow. Lymphoblasts in the marrow were reduced to about 1% and granulopoiesis and erythropoiesis became normal in amount. This state lasted, however, for only a very short time. Clinical and haematological relapse occurred within four weeks in spite of the continued administration of a-methopterin in "maintenance" doses, and the patient died shortly afterwards. In the initial stage of treatment a-methopterin had a pronounced ameliorative effect on leukaemic bone and joint lesions. This effect was also noted in Case 3 and has been observed to occur in cases treated with aminopterin (Dresner, 1950).

Manifestations of a-methopterin toxicity occurred in all cases, and rendered treatment hazardous. The most prominent toxic effects were the development of leucopenia and a greatly increased tendency to bleeding. The onset of leucopenia usually came without warning, and in one case at least was irreversible and proceeded to complete marrow aplasia. In three of the patients the leucocyte counts continued to fall for three to five days after the drug was withdrawn. The amount of a-methopterin needed to influence the marrow in this way varied enormously. The bone marrow in Case 4 became aplastic after only 10 mg. of a-methopterin, whereas 120 mg. was given to Case 1 before there was any significant alteration in the white cell count.

Severe bleeding complicated treatment in every case, and, when present before the administration of a-methopterin, was greatly exacerbated by it. In addition to haemorrhages into the skin and mucosae and bleeding from mucosal surfaces, haemorrhages occurred into the lungs in two cases and into the middle ears in two cases. Haemorrhagic complications were probably responsible for the deaths of six of the patients.

In order to see whether there was any difference in the susceptibility of the leukaemic cells to different antagonists, aminopterin was substituted for a-methopterin in Case 5 after a course of 180 mg. of the latter drug had proved ineffective in controlling the disease. However, in the dosage given, the maximum tolerated, it also proved ineffective in retarding the progress of the illness.

Discussion

From the reports of other workers with a-methopterin it is evident that life may be prolonged in a certain proportion of cases of acute leukaemia in children and that adults are either completely refractory to treatment or, at best, have only short and incomplete remissions. The best results seem to be obtained in children with a subacute type of lymphoblastic leukaemia. Sacks *et al.* (1950) reported three complete temporary remissions lasting 11 to 16 weeks in a series of 20 cases treated —all children. Weber *et al.* (1950) were able to produce haematological or symptomatic improvement in 20 out of 24 children treated with a-methopterin and aminopterin, but remissions were never permanent, and death eventually occurred. Stickney *et al.* (1949) obtained similar remissions lasting up to four months in 5 out of 21 children and in 3 out of 33 adults. In a report by Meyer *et al.* (1950) on the treatment of 11 cases of acute leukaemia with a-methopterin, no particular relation was noted between the effect of the drug and the dosage given, or the age or sex of the patients, and, although the incidence of toxic effects was high, clinical improvement was brought about in only three patients. Although the white blood cells were affected in eight patients, in no instance did the differential count become normal, nor was there a spontaneous rise in haemoglobin or platelets in any case. All authors have noted the failure of further courses of treatment during relapse, and also the rapid development of resistance to increasing amounts of the drugs in patients under treatment.

The increased tendency to haemorrhage in patients treated with folic acid antagonists is perhaps the most serious complication in many of the cases, and was a prominent feature in this series. The haemorrhagic diathesis is not controllable by intravenous protamine

sulphate or toluidine blue (Sacks *et al.*, 1950; Weber *et al.*, 1950), and it therefore seems unlikely that an increased level of heparin-like substances in the blood is responsible, as suggested by Allen *et al.* (1947). Plasma prothrombin levels were estimated in one of our cases and were found to be normal. The increased tendency to bleeding induced by a-methopterin seems to be more severe than that caused by aminopterin. On the other hand, oropharyngeal ulceration, which is almost the rule when effective doses of aminopterin are given (Dacie *et al.*, 1950), was noted in only one of the cases treated with a-methopterin. The extensive gastro-intestinal ulceration found at necropsy in Case 1 appears to be a toxic effect of folic acid antagonists and not a primary leukaemic manifestation. It has been noted in four other cases we treated with aminopterin and in one case treated with a-methopterin by Sacks *et al.* (1950).

Experimentally, a-methopterin has been found effective in significantly prolonging the survival time of mice with the Ak4 strain of transplanted leukaemia, although no direct cytocidal effect, such as characterizes the use of the nitrogen mustards, has been demonstrated (Burchenal, Burchenal, *et al.*, 1949; Burchenal, Johnston, *et al.*, 1949). Weir and his colleagues showed that a crude antagonist of pteroylglutamic acid (folic acid) caused a delay in the appearance of immature cells in the peripheral blood in normal mice, and in Ak4 leukaemic mice it prevented any notable increase in either total white cell count or proportion of blast cells. In mice rendered folic-acid-deficient in this way, the marrow is damaged and the erythroblasts disappear (Weir, Heinle, and Welch, 1948; Weir, Welch, and Heinle, 1949; Thiersch and Stock, 1949). Using a-methopterin, Burchenal, Biedler, *et al.* (1950) confirmed these findings and showed that in the usual therapeutic dosage it caused a slight leucopenia but no change in the differential count of normal mice. In mice with the Ak4 strain of leukaemia its use resulted in a prolongation of survival time, the leucocyte count remaining at approximately normal levels, with reduction in the numbers of abnormal cells and delay in the appearance of leukaemic infiltrations in the viscera and bone marrow.

New light is emerging on the relationship of folic acid and structurally similar antagonists. Sauberlich and Baumann (1948) described a factor necessary for growth of the organism *Leuconostoc citrovorum* 8081, and Sauberlich (1949) indicated a relationship of this factor to folic acid. Recent work indicates that in rat-liver slices the citrovorum factor is formed from folic acid, and that aminopterin both inhibits the conversion and competes with the product (Nichol and Welch, 1950). These workers also found that, although folic acid would not prevent the lethal action of aminopterin on rats, the citrovorum factor completely counteracted the toxic effects of the antagonist.

Burchenal, Babcock, *et al.* (1950) have also shown that, although the prolongation of survival time of leukaemic mice by the administration of a-methopterin can be partially prevented by simultaneous administration of folic acid, the effect of the a-methopterin is completely abolished by small amounts of the citrovorum factor. The citrovorum factor might therefore prove to be effective in countering toxic effects of folic acid antagonists in human leukaemia, although it would also reverse their destructive effect on the leukaemic cells.

The exact mode of action of a-methopterin in leukaemia is not yet fully determined, but the principle involved is presumably the biological competition of structurally related compounds (Woolley, 1947). The possibilities have been fully discussed by Sacks (1949), Weber *et al.* (1950), and Sacks *et al.* (1950). In those cases in which a-methopterin or aminopterin is successful in inducing an initial remission in human acute leukaemia, resistance to further therapy rapidly develops during subsequent relapses. This acquired resistance appears to be similar to the development of "drug resistance" by bacterial cells. That resistance to folic acid antagonists develops in experimental leukaemias in mice has been demonstrated by Burchenal, Robinson, *et al.* (1950) by serial inoculation of leukaemic spleen emulsions in untreated mice and in mice treated with a-methopterin. Although there was no loss of transmissibility in the leukaemic cells as a result of treatment, there was progressive loss of susceptibility to the drug, and by the fifth serial inoculation this was complete, treated animals surviving no longer than the controls. This demonstration of the ability of initially sensitive populations of leukaemic cells to become resistant to a-methopterin may help to explain the eventual failure of treatment in patients with leukaemia. Although resistance may be acquired by the emergence of mutants or through altered metabolism during exposure to the antagonists (see Hinshelwood, 1946), it is also possible that a strain of resistant cells may be present from the beginning in small numbers, and eventually become predominant. Small numbers of leukaemic blast cells persist in the marrow of even the most satisfactorily responding cases.

Summary

The effect of the folic acid antagonist a-methopterin was studied in seven cases of acute leukaemia.

Significant remission was obtained in only one patient, a child with acute lymphoblastic leukaemia, and was of short duration.

Toxic effects were frequent and severe. In addition to effects previously noted with aminopterin, two patients suffered haemorrhage into the middle ear.

We are indebted to Dr. Leo M. Meyer for supplies of a-methopterin. We are most grateful to the staffs of the Departments of Medicine and Paediatrics for allowing us to treat patients under their care.

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TUBERCULOUS MENINGITIS

RESULTS OF TREATMENT WITH STREPTOMYCIN AND INTRATHECAL SULPHETRONE

BY

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At a special unit for the treatment of tuberculous meningitis at Highgate Hospital 48 patients were treated between May, 1948, and November, 1949. These patients were included in a controlled trial of "sulphetrone" given intrathecally. All except three were under 15 years of age. The results of the trial form the subject of this report. Forty-seven cases were proved bacteriologically.

A sulphone derivative (tetrasodium 4:4′-*bis*-(γ-phenylpropylamino)-diphenylsulphone-α; γ; α′-γ′-tetrasulphonate), which has been given the registered name "sulphetrone,"* has been shown to possess high antibacterial activity against the tubercle bacillus with comparatively low toxicity (Brownlee, 1948). Smith, McClosky, and Emmart (1946) have shown that the effect of streptomycin is enhanced by the addition of a sulphone, and a synergistic action of the two compounds has been demonstrated in guinea-pigs (Brownlee and Kennedy, 1948).

Treatment

The intrathecal route of administration was considered advisable because of: (1) the small amounts of the drug found in the brain and cisternal fluid after intravenous or oral administration in animals (Brownlee, 1948); (2) the difficulty of daily intravenous administration in infants and young children; (3) the irregular absorption from the intestinal tract in children, particularly when constipated; (4) the pain caused by intramuscular injection and the relatively large volume required.

Dosage.—The dosage was 200 mg., given with the daily dose of streptomycin intrathecally in the same syringe. Higher doses than this were tried, but were abandoned owing to the greatly increased incidence of convulsions.

C.S.F. and Serum Levels.—With this dosage, cerebrospinal fluid (C.S.F.) and serum concentrations of sulphetrone were very low—0–3 mg. per 100 ml. of serum, and 0–4 mg. per 100 ml. of C.S.F. at 24 hours after injection. Higher levels occurred in a few patients and were accompanied by convulsions.

Toxic Effects.—Toxic effects encountered were convulsions (5 cases), excessive head retraction and opisthotonos (7 cases), mental symptoms (3 cases), and cyanosis (1 case). In five patients the reactions were severe enough to necessitate interruption of treatment. Abnormal blood pigments were not identified and anaemia was not found, although the plasma showed a deep maroon discoloration.

Streptomycin.—The periods during which streptomycin was given to all patients are shown in the Chart. The daily dose was 0.02 g. per lb. (0.45 kg.) body weight in 24 hours intramuscularly and 0.1 g. in 10 ml. of normal saline intrathecally.

Miliary Disease of Lung.—Nine cases showed miliary disease of the lungs—four were in the streptomycin plus sulphetrone series (all survived) and five in the streptomycin only series (two survived).

Results

The 48 patients were all consecutive admissions who had not received any previous treatment. At first, alternate patients (irrespective of age and stage of disease) were given sulphetrone, and the remainder were used as controls. Later, when it was decided to subdivide the cases into groups so as to avoid either series being unduly "weighted" with infants or advanced cases, in whom an unfavourable outcome might be expected, the patients were first classified on admission according to age and stage of disease. Each patient was then allocated to the appropriate division of the six shown in Table I. Within each of these six divisions, alternate cases received streptomycin and sulphetrone, and the remainder received streptomycin alone. By this method an approximately equal number of patients were treated with and without sulphetrone in the two age groups and at each stage of disease on admission. Current admissions were used as control cases, so that any minor advantages in treatment recently developed would apply equally to both series.

TABLE I.—*Showing Age and Stage of Disease in Sulphetrone and Control Groups*

Stage of Disease:	Early		Middle		Advanced		Total
Age Group:	Under 3 yr.	Over 3 yr.	Under 3 yr.	Over 3 yr.	Under 3 yr.	Over 3 yr.	
Streptomycin (control group) ..	5	3	3	8	2	2	24
Streptomycin and sulphetrone (sulphetrone group) ..	4	2	2	10	2	4	24

The results of treatment are shown in Table II. All patients have been observed for a minimum period of

*We wish to thank Messrs. Burroughs Wellcome and Co. for supplies of sulphetrone in a form suitable for intrathecal injection.

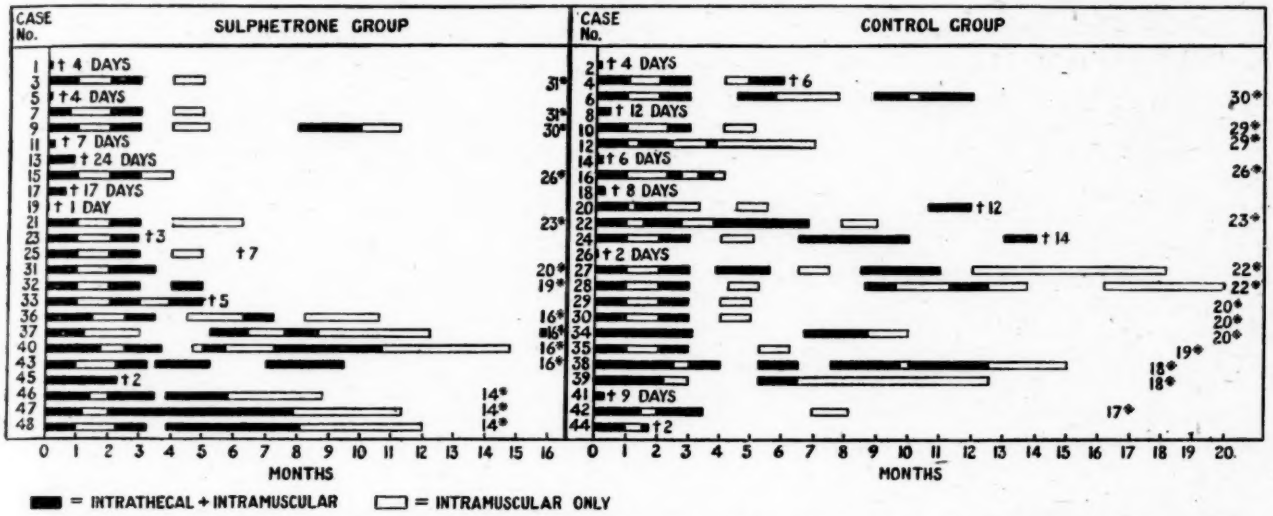

Chart showing periods, up to December, 1950, during which streptomycin was given to all cases. Cases are numbered serially according to date of admission. *Figures with an asterisk denote survival periods in months from start of treatment. † = Death.

twelve months from the start of treatment. The survival rate in the two groups was the same. In addition to the crude survival rate no appreciable clinical difference was found between the two groups.

TABLE II.—*Results of Treatment (Survivors After 12 Months' Minimum Observation)*

Stage of Disease*:	Early		Middle		Advanced		Total
Age Group:	Under 3 yr.	Over 3 yr.	Under 3 yr.	Over 3 yr.	Under 3 yr.	Over 3 yr.	
Survivors:							
Streptomycin ..	4	2	0	7	0	1	14 (58%)
Streptomycin and sulphetrone ..	3	2	1	8	0	0	14 (58%)
Total	7	4	1	15	0	1	28 (58%)

*The criteria for classification of patients according to the stage of disease on admission are those recommended by the Medical Research Council (1948).

Discussion

In view of the close similarity of the composition of the "treatment" and "control" series in terms of age and stage of disease, the finding of exactly similar survival rates in the two groups is certainly significant and confirms our clinical impression that sulphetrone, when injected intrathecally, is of no value in the streptomycin treatment of tuberculous meningitis.

When this trial was started, no other reports of the use of sulphetrone intrathecally were available. Two reports have since been published. Fouquet *et al.* (1949) treated an unstated number of patients with the addition of a sulphone (diaminodiphenylsulphone) intrathecally. They reported 59% cured among the sulphone-treated group, and 53% among the controls, treated with streptomycin alone. Rist and Cottet (1949) treated a series of 20 patients with the same sulphone intrathecally. They used a dose of 2–3 mg. per kg. body weight daily. During rests from intrathecal treatment they gave a total daily dose of 3–4 mg. per kg. body weight by mouth. A control series of 39 patients was treated with streptomycin alone. Patients who died during the first month of treatment were excluded. The control group showed a survival rate of 52%, as against 72% in the sulphone-treated group. The authors attributed the improved results in the latter group to the reduction in deaths due to streptomycin-resistant strains of tubercle bacilli, during the fourth to sixth month of treatment.

In the 48 cases covered by the present report, significant streptomycin resistance* has been encountered as follows: In one patient, in bacilli isolated on the thirteenth day of treatment (thousandfold resistance); in one patient at the eleventh month of treatment (thousandfold resistance); in a third patient at the seventh month of treatment (160-fold resistance). None of these patients was treated with intrathecal sulphetrone, but the incidence of resistance is clearly too low to permit any conclusions to be drawn concerning the effect of sulphetrone in this respect.

Summary

A controlled trial of intrathecal sulphetrone in addition to streptomycin for tuberculous meningitis is reported. The dose of sulphetrone given was 200 mg. daily.

Toxic reactions necessitated interruption of treatment in 5 out of 24 cases treated.

The crude survival rate after a minimum of 12 months' observation was the same (58%) in both the treated and the control groups. The results combined with our clinical observations do not indicate that sulphetrone injected intrathecally is of value when added to the streptomycin treatment of tuberculous meningitis.

We wish to thank the following for advice and help: Dr. S. Yudkin, paediatrician, Whittington Hospital; Dr. J. M. Alston, pathologist, Archway Group Laboratory; Miss M. F. Crowley, biochemist, Archway Group Laboratory; the numerous laboratory technicians who helped with the pathological work; Dr. C. D. Coyle, medical superintendent, Whittington Hospital, and Sister S. E. Robinson and the nursing staff who had the care of the patients treated in the unit.

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*Streptomycin resistance is defined in relation to the standard strain H37Rv, and we have taken 32-fold resistance as being probably the minimum significant level. The clinical significance of resistance less than several hundredfold is still not established.

TUBERCULOUS MENINGITIS TREATED WITH STREPTOMYCIN

FOLLOW-UP OF SURVIVORS FOR A MINIMUM OF TWO AND A HALF YEARS

BY

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In February, 1949, two of us (J. R. and A. F. M.) reported the results of the treatment of 54 patients for tuberculous meningitis. These patients were admitted to a special unit during the period July, 1947, to May, 1948. The minimum observation period at the time of that report was eight months (Rubie and Mohun, 1949). The survivors have now been observed for a minimum period of two and a half years, and it is felt that a report on the original series after this longer period would be of value. The maximum observation period is three and a half years.

Results

The results are summarized in the Table. The original 18 survivors have been reduced to 16 (30%), two having died. Three patients relapsed, but have recovered after further treatment.

The periods for which streptomycin was given for the relapses are shown in the Chart. The daily dose was the same as mentioned in the previous report.

Sequelae shown by the survivors are deafness in two children (partial in one), a minimal hemiplegia in one child, retarded development in one, and an intellectual defect in one.

Audiometric and vestibular tests have been carried out on 14 of the 16 survivors. All showed complete loss of vestibular response during caloric tests, yet none of them show clinical ataxia in a good light. Some patients, however, were slightly ataxic with the eyes closed or in the dark. Audiometric tests revealed a marked hearing loss in Case I and a loss up to 50 decibels in Case 11. In the remainder the audiograms were normal.

Later manifestations of non-meningeal tuberculosis, presumably due to sporadic haematogenous dissemination of tubercle bacilli, have occurred in two recovered cases (Nos. 1 and 11). These have not been accompanied by any evidence of recrudescence of meningitis.

Although the number of cases is small, there is no evidence to show that patients who present radiological

*Details of the 18 Original Survivors (December, 1950)**

Case No.	Age at Onset (Years)	Stage on Admission	Chest X-ray	Period of Observation from Start of Treatment (Months)	Method of Treatment	Course
1	4 6/12	E	P.C. Mil.	41	I.T. and I.M.	Latest C.S.F. normal, but previous small fluctuations in cells and protein. Deaf. Ataxia not now apparent. Developed synovial tuberculosis of left wrist 28 months after onset of meningitis; this is responding to orthopaedic treatment
2	4 7/12	M	Mil.	41	,, ,,	C.S.F. normal. Full recovery. Ataxia not now apparent. Attends normal school
3	8 8/12	E	P.C.	41	I.M.	Latest C.S.F. normal, but previous small fluctuations in cell count. Full recovery. Tuberculous left knee was treated with a splint (now discarded) for 3 years from onset of meningitis. Attends normal school
4	6 1/12	M	,,	41	I.T. and I.M.	C.S.F. normal. Full recovery. Attends normal school
5	6 6/12	E	Nil	40	,, ,,	C.S.F. normal. Full recovery. Attends normal school
6	3 4/12	E	P.C.	39	,, I.M. ,,	Latest C.S.F. normal, but previous small fluctuations in cell count. Full recovery. Tuberculous spine was treated with a spinal jacket (now discarded) for 3 years from onset of meningitis. Attends normal school
7	12 11/12	M	Nil	39	I.M.→I.T.	Full recovery. C.S.F. showed a persistently raised protein (50–100 mg. per 100 ml.). Attended a school for backward children before illness and has returned to same school. No evidence of deterioration
8	15 6/12	E	Mil.	39	I.T. and I.M.	C.S.F. normal. Full recovery
9	10/12	M	P.C.	37	,, ,,	Latest C.S.F. normal, but previous small fluctuations in protein content. Physical and mental development retarded in comparison with twin sister
10	10 4/12	A	Nil	35	,, ,,	C.S.F. normal. She shows an intellectual defect and maladjustment of hysterical type, possibly precipitated by tuberculous meningitis
11	11	E	Mil.	33	,, ,,	Full recovery, with normal C.S.F. 11 months after onset of original illness. Relapse 8 months later followed by full recovery after further treatment, with normal C.S.F. 12 months later (31 months after onset of original illness). During the final period of intramuscular treatment she developed a tuberculous abscess over the sternum which resolved satisfactorily. Partial deafness
12	17 8/12	E	Nil	18	,, ,,	Previously reported as full recovery with normal C.S.F. Relapsed 13 months after onset of original illness and died 5 months later in spite of further treatment. Necropsy revealed a cortical tuberculoma
13	10	M	Nil	32	,, ,,	Full clinical recovery. C.S.F. has shown fluctuation in cells (3–26 per c.mm.) and in protein (60–160 mg. per 100 ml.); it has not been entirely normal at any single examination. Attends normal school
14	6	M	Nil	32	,, ,,	C.S.F. normal. Residual minimal right hemiplegia. Attends a normal school
15	5 6/12	E	Mil.	32	,, ,,	C.S.F. normal. Full recovery. Attends a normal school
16	10 3/12	E	,,	31	,, ,,	Previously reported as full recovery with normal C.S.F. (11 months). Relapsed 3 months later and responded to further treatment with full recovery and normal C.S.F. 14 months later (28 months after onset of original illness). Attends normal school
17	5 1/12	M	P.C.	13	,, ,,	C.S.F. never became normal. He died with a recrudescence of the disease 13 months after onset of illness
18	4 11/12	E	,,	31	,, ,,	Previously reported as full recovery with normal C.S.F. (9 months). Relapsed 4 months later and responded to further treatment with full recovery and normal C.S.F. 14 months later (27 months after onset of original illness). Attends normal school

E = Early case. M = Middle case. A = Advanced case. P.C. = Primary complex. Mil. = Miliary disease of lungs. I.T. = Intrathecal streptomycin. I.M. = Intramuscular streptomycin. I.M.→I.T. = Intramuscular followed by intrathecal streptomycin. I.T. and I.M. = Intrathecal and intramuscular streptomycin together.

* At April, 1951, the condition of the survivors is unchanged.

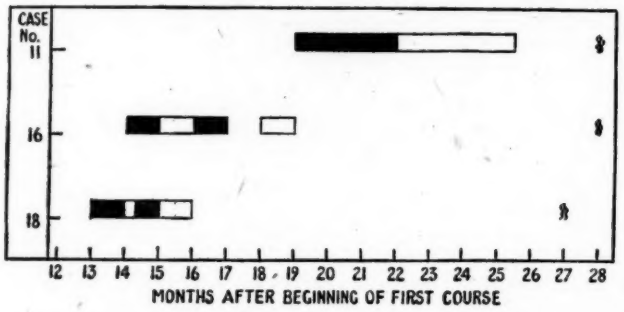
CASE No.
11
16
18
12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28
MONTHS AFTER BEGINNING OF FIRST COURSE
$ = C.S.F. NORMAL
= INTRATHECAL + INTRAMUSCULAR
= INTRAMUSCULAR ONLY

Chart showing periods during which streptomycin was given for relapse. The criteria of C.S.F. normality have been: cells—not more than 5 per c.mm.; protein—not more than 40 mg. per 100 ml.; chlorides—not less than 720 mg. per 100 ml.; sugar—not less than 45 mg per 100 ml.

signs of miliary tuberculosis of the lungs associated with meningitis are subsequently more liable to relapse.

Conclusions

A relapse may occur in cases of tuberculous meningitis after full clinical recovery and return of the cerebrospinal fluid (C.S.F.) to normal. No precipitating cause for relapse has been found.

Occasional slight abnormalities of the C.S.F. up to two years after cessation of all treatment may be unaccompanied by any other evidence of activity. The significance, if any, of these variations can be assessed only by a further period of observation, the length of which has not yet been determined. We therefore do not feel able to regard a patient as finally cured and requiring no further observation even after two and a half years from the cessation of streptomycin treatment.

Summary

A follow-up report is presented on the condition of the survivors in a series of cases of tuberculous meningitis previously reported.

Of the 18 original survivors, two have died, and three have relapsed but recovered after further treatment. Two developed non-meningeal tuberculous lesions which responded to treatment. The survival rate has been reduced to 30% (16 cases).

Slight variations in the C.S.F. of the survivors have been found, but their significance could not be determined. A further period of observation is necessary.

We wish to thank the following for advice and help: Dr. J. M. Alston, pathologist, Archway Group Laboratory; Dr. S. Yudkin, paediatrician, Whittington Hospital; Dr. C. D. Coyle, medical superintendent, Whittington Hospital; Dr. A. S. Walker, of the Institute of Otology and Laryngology, for audiometric and vestibular tests; and Sister S. E. Robinson and the nursing staff who had the care of the children treated in the unit.

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The Minister of Health (Mr. H. Marquand) recently visited a blood-donor session at a London hospital and himself gave a pint of blood. In a short speech he remarked that hospitals to-day used nearly 1,000 pints of blood a day, a fiftyfold increase on pre-war. Another 200,000 blood donors were needed to meet all the demands now being made on the National Blood Transfusion Service.

ORF IN LONDON

BY

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The word "orf" is derived from the Saxon for cattle; it is now applied to contagious pustular dermatitis, a malady of sheep that is well recognized by those who deal with these animals.

Hansen (1879), Hatziolos (1929), Peterkin (1937), Schoch (1939), and others have described the lesions of orf in man, and the condition is now well recognized as being common in many sheep-rearing localities; in southern England, and especially in London, it has rarely been seen. For this reason, and because the disease is likely to be mistaken for a simple pustular infection, the following cases are recorded, all having occurred within three months (November, 1950, to January, 1951) in London.

Natural History

In sheep, orf is characterized by ulcerative and pustular lesions of the skin and mucous membranes. It occurs particularly in lambs under 1 year old. The mortality rarely exceeds 1% (National Veterinary Medical Association publication, 1944). Human orf follows contact with infected animals, whether dead or alive. In the latter the saliva seems to be particularly infectious, and there is evidence that dried saliva crusts may also harbour the infection for several months (Glover, 1929). The incubation period has never been accurately assessed, but it is short, and is probably between three and seven days.

The infected person usually has a single lesion situated on the arm or hand, or occasionally it may be on the face; sometimes multiple lesions are seen (Blakemore, Abdussalam, and Goldsmith, 1948).

The lesion consists of a raised nodule, 1–3 cm. in diameter, which usually is ulcerated at its summit. The shallow ulcer is surrounded by dead, white, soggy skin, and the whole gives the appearance of a granuloma in the centre of a blister or pustule. When explored, as it not infrequently may be, pus is not obtained, and only a little blood exudes. Pain is slight and general toxic symptoms are mild or absent; lymphangitis and regional lymphadenopathy may be present; but all are less pronounced than would be expected if the lesion were of pyococcal origin.

The infection is self-limiting: resolution occurs in five to eight weeks, and is completed with remarkable rapidity when once it starts.

The causative organism is a virus which has been isolated by several workers and found to be morphologically (by electron microscopy) and immunologically identical with the virus found in contagious pustular dermatitis of sheep; further, the disease has been experimentally transmitted to a human volunteer (Blakemore, Abdussalam, and Goldsmith, 1948). Lyell and Miles (1950) reported having cultivated the virus from man on living chick embryos; subsequently they infected the lamb with the virus, the animal developing typical contagious pustular dermatitis. Thus, instead of having merely circumstantial evidence of the connexion between orf in man and the infection in sheep, the relationship can now be regarded as proved.

In the present series, Cases 1–6 were porters in Smithfield meat market; each had a single lesion on the hand. They were all experienced in handling meat and had handled sheep's heads on many previous occasions, but they stated that they had never previously had similar lesions. They all worked in one particular depot, which had been receiving sheep's heads from the Peebles, Dumfries, and Kelso areas of Scotland. Although the heads were contained in thin muslin-like bags, the men often scratched their skin on the teeth which protruded through the fabric.

Case Reports

Case 1 (Fig. 1).—No treatment was given. The lesion resolved in eight weeks, leaving a bluish scar and an enlarged and tender regional lymph gland which persisted for a month after healing.

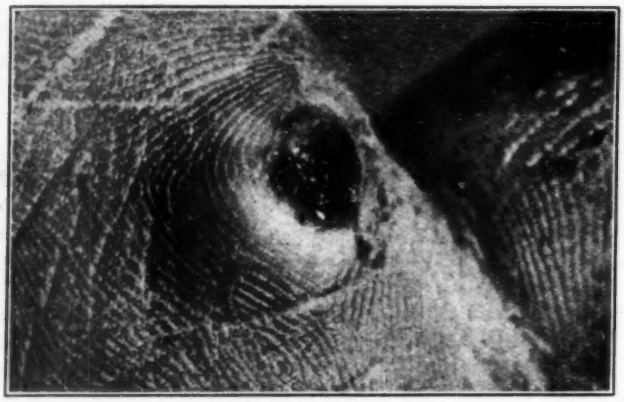

FIG. 1.—The lesion in Case 1.

Case 2.—The lesion was opened nine days after its onset. Bacteriological examination gave a scanty growth of coliform bacilli only, and material was taken for virus identification. No treatment was given, and the lesion healed in five weeks.

Case 3 (Fig. 2).—This patient was treated with chloramphenicol, 500 mg. six-hourly, for seven days. The lesion took five weeks to clear up. When comparison was made with untreated cases it was concluded that treatment did not affect the course of the lesion.

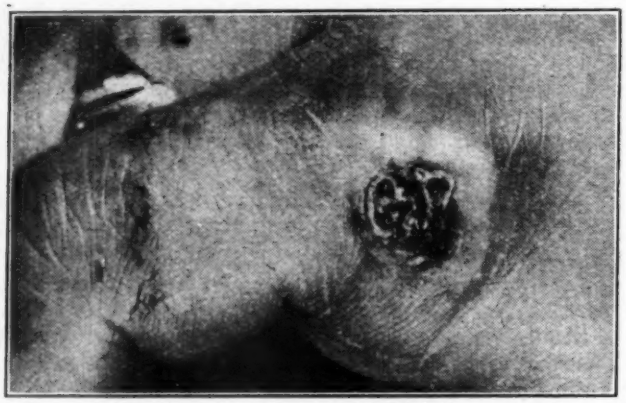

FIG. 2.—The lesion in Case 3.

Cases 4, 5, and 6.—No treatment was given. The lesions cleared up spontaneously in six, five, and seven weeks, respectively.

Case 7.—A butcher gave a history of having handled sheep's heads intermittently over a long period. In particular, a batch was received from Scotland three days before he noticed two spots appear—one on the forefinger and one on the fifth finger of his left hand. These became larger and ulcerated. Chloramphenicol, 500 mg., was given six-hourly, but no change in the lesions occurred. As this patient had two lesions, one was treated by the application of 3% "aureomycin" ointment and the other was untreated, serving as a control. No difference occurred in the two lesions; both disappeared in six weeks.

Case 8.—A housewife who complained of a lesion on the back of the middle finger of her right hand gave a history of having handled sheep's heads 7 days and 14 days before the onset. The case was not seen until late in its course. In the fifth week, after 500 mg. of aureomycin had been given six-hourly for three days, the lesion dried up and healed. It was considered that, as treatment was started so late in the course of the illness as compared with the untreated cases, it was unjustifiable to attribute resolution to the therapy.

Comment

The sheep's heads concerned came from the sheep-rearing country of Southern Scotland, where orf is enzootic, but it is not thought that the condition has been any more active during the past year than in previous years (Duthrie and Leslie, 1951, personal communication).

Examples of orf have been found in three groups of people who come into contact with infected animals after they have left the slaughterhouses—meat porters, butchers, and housewives. In the first two groups and in farmers the diagnosis may be suggested by the occupational history. In the case of housewives the connexion with sheep will usually be less obvious, and because of this the diagnosis may have been missed in the past.

There is evidence that the natural course of the infection is between five and eight weeks and that chloramphenicol does not affect it. So far there is insufficient evidence of the effect of aureomycin.

The importance of recognizing this condition lies in differentiating it from pyococcal infections which will benefit from surgery and the use of the more readily available antibiotics, since orf does not.

Summary

Eight cases of orf are described. All occurred in London—six in meat porters, one in a butcher, and one in a housewife. All had handled sheep's heads which came from areas of Scotland where orf is known to be enzootic. The natural course is five to eight weeks, and was not found to be altered by the treatment given.

I am indebted to Dr. R. M. B. MacKenna and to Dr. Brian Russell for permission to publish their cases; also to the photographic department of the Medical College of St. Bartholomew's Hospital for the photographs.

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The Operation of a Central Syringe Service (free from 9, Blackfriars Street, Salford, 3) is a well-got-up booklet which analyses the requirements laid down by M.R.C. *War Memorandum No. 15* on the use and care of syringes, and shows both in text and by pictures of the service at the Sheffield Royal Infirmary how these requirements may be met.

THE RADICAL CURE OF INGUINAL AND FEMORAL HERNIA WITH A POLYTHENE INSERT

BY

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This paper records the experience gained in the use of "polythene" in the radical cure of inguinal herniae since August, 1946, and its application in the cure of certain femoral herniae. I carried out 103 herniorrhaphies in one surgical unit at the Manchester Royal Infirmary from August, 1946, to February, 1950. Out of this number 61 were polythene repairs, and, with the exception of one case which was lost through change of address, all were seen regularly at the follow-up clinic. The results are set out in the accompanying Table.

The series as a whole is a selected one and contains only those herniae which, after general assessment, were found to require a major repair and might therefore be suitable for a polythene insert. At operation 24 out of 75 inguinal herniae were found to require only excision of the sac, narrowing of the internal ring, and simple darn of the transversalis fascia with nylon.

No arguments are put forward here for introducing polythene in the repair of these difficult herniae, but it has been the aim to reduce the recurrence, rejection, and morbidity rates to *nil*. This aim has so far been achieved, with the exception of one case in which a persistent sinus led to the removal of the plate. Some of the older patients were persuaded to have a polythene plate repair after wearing a truss for many years, and all active workers have returned to their occupations within six weeks of operation.

Polythene

This long-chained polymer of ethylene was first introduced in this country by the I.C.I. in 1933. As it is made by a melting-out process which does not involve the use of plasticizers, it produces a minimal fibrous tissue reaction when introduced into the body.

To the naked eye polythene has a waxy, white appearance and feels slightly soapy to the touch. It repels water, on which it floats, and is light and cheap. In sheets 1/16 in. (0.16 cm.) thick it is quite firm, but can be bent without breaking. It is easily cut by scissors and can be perforated by a Mayo needle. The degree of polymerization of the ethylene molecules changes the physical characteristics. Grade 200, with a molecular weight of 12,000 and a melting-point of 115° C., was chosen for implantation in the tissue, as in 1/16-in. sheet form and at body temperature it is capable of withstanding normal muscular strains. Polythene is non-opaque to *x* rays and cannot be sterilized by autoclaving. It is best sterilized by soaking it in perchloride of mercury 1 in 1,000, biniodide of mercury 1 in 1,000, lysol, or "dettol."

The plastic is lighter than water, so it must be weighted to the bottom of the solution in which it is

	Polythene and Combined		Other Methods	
	Inguinal Hernia	Femoral Hernia	Inguinal Hernia	Femoral Hernia
No. of cases	45	10	22	17
Bilateral herniae	6	—	2	1
Total herniae	51	10	24	18
Repairs	44 polythene 7 combined	— 10 combined	Nylon repair T. fascia and int. ring	Lockwood using nylon
Male	42	4	16	7
Female	3	6	6	10
Right	22	7	9	12
Left	29	3	15	6
Ages in years	31–85	38–74	22–77	36–77
Average	52	52	43	53
Strangulated	4	6	1	10
Resections	None	1	None	3 (through separate abdominal incision)
Types:				
Oblique	26	1 with O.I.H.	17	—
Direct	9	1 with D.I.H.	2 bilateral	—
Saddle-bag	1	—	1	—
En glissade	3	—	—	—
Recurrent hernia	6 3 oblique 1 en glissade (following herniorrhaphy and orchidectomy)	2 —	1 (recurrent oblique)	None — —
Anaesthesia:				
Spinal	35	7	18	11
General	5	3	2	1
Local	5	—	2	5
Complications	1 sinus (persistent) 1 mild infection 1 haematoma	None	1 sinus (temporary) 1 hydrocele	1 long saphenous varix
Recurrences	None	,,	None	1 D.I.H. same side 3 O.I.H. ,, ,,
Appearances of hernia on opposite side	6	,,	1	1
Deaths	None	1 strangulated non-resection case	None	1 strangulated (non-resection case)
Follow-up	All cases	All cases	All cases	1 case lost through changed address

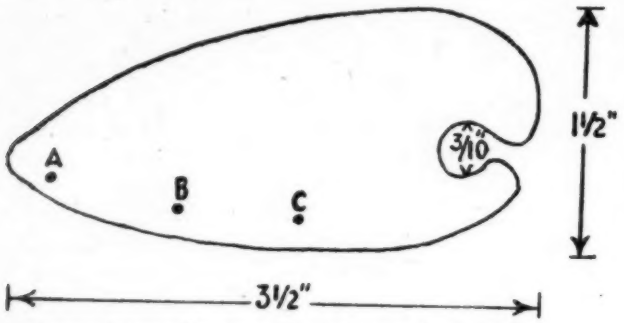

Diagram showing average size of polythene insert. 1/16-in. thick plate, polythene I.C.I., Grade 200. A, Stitch hole for suture to Cooper's ligament. B, Stitch hole for suture to deep femoral arch. C, Stitch hole for suture to Poupart's ligament.

being sterilized by wrapping it in lint. The size of plate used to replace the transversalis fascia in the cure of inguinal and femoral hernia is shown in the diagram.

The Combined Repair

The incision is made in Langer's tension lines beginning over the outer third of Poupart's ligament and extending inwards as far as the external ring, where the incision curves downwards for 1 in. (2.5 cm.). The skin flap is reflected downwards, exposing the inguinal and femoral rings. If a femoral sac is present it is dissected out and reduced by incising Hey's ligament and the constriction ring in the neck of the sac where necessary. The external oblique is next divided in the direction of its fibres and the upper and lower flaps are turned back. The cremaster muscle along with the ilio-inguinal nerve is now removed from in front and behind the cord, exposing the structures of the cord, the free lower arching border of the internal oblique muscle, the conjoint tendon, transversalis fascia, Poupart's ligament, the internal ring, and any sacs which may be present. This necessitates ligation and division of the cremasteric vessels as they pierce the transversalis fascia opposite the deep epigastric vessels.

The oblique sac is next dissected out and the peritoneum liberated in all directions for 1½ in. (3.8 cm.) from the fascial attachments at the internal ring. As the sac is usually a wide-necked structure, it is cut off and the opening is closed by a running catgut stitch. The finger is then passed medially behind the deep epigastric vessels and transversalis fascia in the extraperitoneal fat, and the transversalis fascia incised as far as the attachment of the conjoint tendon to the pectineal line. The deep epigastric vessels are divided and ligated during this manœuvre. The upper flap of the transversalis fascia is reflected upwards and the peritoneum and extraperitoneal fat are stripped off the lower flap, thus exposing the femoral canal. If the latter structure contains a sac or admits the tip of the index finger, the lower flap of the transversalis fascia is turned back and sutured to Cooper's ligament by a fine nylon running stitch. An abnormal obturator artery may need dividing.

Recent experience in closing the femoral ring by this method has shown that occasionally the transversalis fascia is not strong enough ; in these cases it is necessary, after turning back the lower flap of the transversalis fascia, to strengthen it by a nylon darn.

This procedure prevents Poupart's ligament from being pulled out of line and gives adequate closure of the femoral canal without compressing the femoral vein. The polythene plate is next placed in the extraperitoneal fat. The lower border of the plate is fixed by stitching it medially to Cooper's ligament just behind the insertion of the conjoint tendon into the pectineal line, and laterally to Poupart's ligament opposite the deep epigastric vessels. The upper flap of the transversalis fascia is now brought down and sutured to Cooper's ligament, Gimbernat's ligament, the deep femoral arch, and Poupart's ligament by a running catgut No. 0 suture, stitching medio-laterally in the above order. The cord is replaced and the external oblique and skin are sutured in the usual manner.

It is stressed that this repair does not destroy any muscle tissue other than the cremaster which is excised, and no stitches are inserted into the free arching border of the internal oblique. Thus the sphincteric mechanism of Sir Arthur Keith is left intact. The new internal ring is displaced outwards for 1 in. (2.5 cm.) under the strong arching fibres of the transversalis and internal oblique muscles, thus increasing the obliquity of the inguinal canal. The weak area of the transversalis fascia below the conjoint tendon, which has been partly used to close the femoral canal, is replaced by the strong polythene plate.

Anaesthesia and Post-operative Treatment

As this operation involves an extensive dissection with relaxed muscles and fascial planes, spinal anaesthesia is still the method of choice. General anaesthesia with curare finds a place in certain strangulated cases, as does local analgesia in the older age groups.

Patients are instructed in breathing exercises in the immediate post-operative period ; smoking is forbidden. From the first post-operative day they take part in the routine ward exercises, which are gradually increased in range until the ninth post-operative day, when the patients get up. Older patients get up as soon as they feel able, and this is usually about the third day. Patients are allowed to go home by ambulance on the tenth post-operative day and are instructed to continue exercises and gradually to increase the period of remaining up until they are up and about fully dressed three weeks after operation. After six weeks' convalescence patients return to light duties. Three months after the operation they begin full duties.

Indications and Results

Sixty-one polythene repairs have been performed since August, 1946, and every case has been carefully followed up. No patient has complained of any pain in the wound, and no plate has moved, fragmented, or caused secondary suppuration. Most patients notice a little numbness at the inner angle of the wound, but none have complained about this. No testicular atrophy, hydrocele, or varicocele has been seen. Thus the follow-up, up to three and a half years, has been very gratifying.

No recurrences have been seen, but eight herniae have appeared on the opposite side, and three oblique inguinal herniae on the same side have been noted within two years of performing Lockwood's repair for femoral hernia. As these herniae are directly due to altering the mechanism of the inguinal canal, they ought to be classified as recurrent herniae, thus giving a recurrence rate of 17%. This rate is sufficient to condemn the low operation of Lockwood in those patients who might be expected to have a preformed oblique sac. The

combined operation is therefore reserved for large and long-standing femoral hernia, recurrent hernia, pre- and post-vascular hernia, and femoral hernia in young adult males who have heavy occupations or chronic chest trouble.

Three wound infections occurred in this series, one of which led to a persistent sinus. The polythene plate was removed after being in place six months. This was remarkably easy to perform, as the plate had simply become encapsulated in a smooth fibrous tissue envelope the thickness of brown paper. No further repair was necessary, and follow-up of this patient three years later showed no recurrence.

Summary

A personal consecutive series of 103 inguinal and femoral herniae is reviewed in which 61 polythene repairs were performed. The detailed results are given with the follow-up up to three and a half years. No recurrences, in the generally accepted sense, have occurred to date. The operation of Lockwood gives rise to a "recurrent" oblique inguinal hernia in about 17% of cases and ought not to be used as a routine. The combined repair is described in detail.

I would like to thank Mr. A. Graham Bryce for allowing me to carry out this work in his unit at the Manchester Royal Infirmary, also to Messrs. I.C.I., Ltd., for further chemical details and for supplying the polythene sheets.

Medical Memoranda

Essential Thrombocytopenia, Gastro-intestinal Haemorrhages, and Peptic Ulceration as a Diagnostic Problem

Essential thrombocytopenia may become manifest by repeated haemorrhages from the gastro-intestinal tract, but the following case shows that this should not obscure the possibility that a coincidental condition is causing the bleeding.

Case Report

The patient, a man aged 50, was well until the age of 12, when he began to have severe nose-bleeding, which persisted until he was 18. At this age he developed an effusion into the left ankle-joint following a slight injury: this effusion was proved to be haemorrhagic when it later ulcerated through the skin, and in 1922 required surgical removal. At this time he was thought to be suffering from haemophilia, but his family history had no record of any relations with a similar disease. He remained well for two years, but in 1924 had his first haematemesis, and this was repeated in 1925 and 1926. These haemorrhages were not preceded by any abdominal pain. After the last haematemesis he entered the Liverpool Royal Infirmary. His blood count then was red cells, 4,700,000; haemoglobin, 75%; platelets, 127,000. A diagnosis of essential thrombocytopenia was made, for which the patient was treated by splenectomy.

He remained well until 1934, when he developed indigestion, which occurred about four times a year in attacks lasting three to four weeks at a time. An upper abdominal ache came on two hours after food but never awoke him at night, and it was relieved in twenty minutes by taking food or alkali. This indigestion was associated with all his subsequent intestinal haemorrhages. So far as he can remember, these occurred in the following manner: 1938, haematemesis (a barium meal two months later was said to have shown no abnormality); 1941, melaena; 1943, melaena (barium meal again said to be normal); 1944, melaena; 1945, melaena; April, 1948, haematemesis; December, 1948, haematemesis; 1949, melaena and haematemesis.

In 1946 he attended a hospital because of a tumour of the left side of the skull, in the parietal area, which had been developing over the previous eight years. Blood investigations at that time gave the following results: red cells, 4,600,000; haemoglobin, 92%; white cells, 12,200; platelets, 32,000; bleeding time, 9½ minutes; coagulation time normal. This tumour was removed in 1948, and was found to be a large haematoma which had eroded the bone. Later in the year the area had to be skin-grafted after the removal of a further clot.

His most recent illness started early in September, 1949, with a further attack of indigestion, which continued until on the 20th he passed a melaena stool. His indigestion then became more severe and he started to vomit. A small haematemesis occurred on September 27, and was repeated several times on October 2, when he vomited about two pints (1.14 litres) of blood. He was admitted to the West Middlesex Hospital that night.

Examination showed him to be very exsanguinated and the blood pressure at first was unobtainable, but when he had rallied it was found to be 154/88. Later examination showed no abnormality in any system. No telangiectases were seen on the skin, but there were several scars—one from the splenectomy in the left subcostal region, one in a depressed area in the left parietal region, and a third on the left ankle, which showed slight limitation of movement.

He was transfused immediately on admission, four pints (2.27 litres) of blood being given between 8.45 p.m. and 5 a.m. the next day, when he was greatly improved. Over the next few weeks the following investigations were made:

Blood Counts.—October 5 (immediately after transfusion): Red cells, 2,900,000; haemoglobin, 7.6 g. (52%); M.C.H., 26 $\mu\mu$g.; 12% late normoblasts; white cells, 11,600 (polymorphs 68%, lymphocytes 28%, monocytes 1%, eosinophils 3%). Platelets were too scanty for accurate estimation. November 18: Red cells, 4,500,000; haemoglobin, 11.8 g. (80%); M.C.H., 26 $\mu\mu$g.; bleeding time, 1 minute; coagulation time, 1½ minutes.

Radiographs.—October 28: A barium meal showed a small gastric ulcer on the lesser curvature of the stomach; a barium swallow had revealed no abnormality.

Gastroscopy.—On November 10 gastroscopy showed a small gastric ulcer at the angularis, with shelving sides and rugae radiating from it.

Consideration of the case suggested that all the intestinal bleeding since 1938, when his indigestion started, was probably from peptic ulceration, and that surgical treatment was clearly indicated.

On November 22 he was operated on under regional analgesia after a transfusion of one pint (568 ml.) fresh blood. The anterior wall of the duodenum was scarred from previous ulceration, and an active gastric ulcer ½ in. (1.25 cm.) in diameter was found on the posterior wall of the stomach near the lesser curvature. No splenunculi were seen. A partial gastrectomy of the Polya–Hofmeister type was performed. Bleeding was not excessive during the operation, although the clots did not retract well, and the post-operative course was uneventful except that there was a slight vomit of blood-stained material on the second day.

A blood examination made on December 6 showed: Red cells, 4,750,000; haemoglobin, 11.9 g. (80%); M.C.H., 25 $\mu\mu$g.; white cells, 12,800 (polymorphs 47.5%, lymphocytes 48%, monocytes 2.5%, eosinophils 2%); platelets, 199,000; bleeding time, 1 minute; coagulation time, 1 minute 15 seconds.

Since the operation the patient has had no symptoms and no haemorrhage, but it is still too soon for a final assessment of the result.

Comment

The interest in this case lies in the delay in the diagnosis, which resulted in many serious haemorrhages, the last of which was nearly fatal. This delay was

caused by the knowledge that bleeding in essential thrombocytopenia may occur repeatedly from one site, such as the gastro-intestinal tract, and may relapse after splenectomy, while haemorrhage from coexisting peptic ulceration has rarely been reported. A similar case was referred to by Giffin (1936). A patient of his, aged 52, who had been treated for essential thrombocytopenia by splenectomy, died nine months later from haemorrhage from a duodenal ulcer. Giffin does not state, however, whether the diagnosis was made in life, and does not refer to the case as a diagnostic problem.

In the present case the three haematemeses which occurred before the splenectomy were almost certainly due to essential thrombocytopenia. After operation there was no further bleeding for twelve years. When haemorrhage restarted the site was the same, and so relapse of the essential thrombocytopenia was diagnosed, and this opinion was strengthened by the two negative barium meals. However, the history of dyspepsia, which had not been associated with the earlier haemorrhages but preceded all the later ones, should have suggested the correct diagnosis.

On consideration it is clear that gastro-intestinal haemorrhage, when occurring in association with essential thrombocytopenia, and especially if relapsing after splenectomy, requires most careful investigation to exclude coincidental chronic peptic ulceration. Further, if bleeding occurs from a peptic ulcer and there is coexisting thrombocytopenia, any haemorrhage is likely to be severe because of the sparsity of the platelets; and this makes complete cure of the ulcer so important that surgery may well be the treatment of choice.

My thanks are due to Dr. M. M. Deane for the gastroscopy, to Mr. W. J. Ferguson for operating, and to Dr. J. A. Torrens for permission to publish the case.

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REFERENCE

Giffin, H. Z. (1936). *Int. Clin.*, **4**, 95.

Unusual Length of Plastic Tubing in the Urinary Bladder

The discovery of foreign bodies of various sizes and shapes in the urinary bladder is by no means a rarity, but the following case seems worthy of record.

Case Report

A boy aged 15 was admitted to hospital with a two-year history of *Bact. coli* infection of his urinary tract; despite treatment with alkalis and sulphadimidine the urine had never remained completely sterile. Physical examination was negative. There was no tenderness over the hypogastrium or over either renal area, but microscopical examination of a mid-stream specimen of urine revealed a heavy deposit of pus cells, and *Bact. coli* on culture. The non-protein nitrogen was 33 mg. per 100 ml. The report on a straight *x*-ray film of the renal tract stated: "There is a curled-up tube about the size of a ureteric catheter lying in the bladder; an intravenous pyelogram shows both kidneys to be secreting well, with a normal pelvis and calices on each side." In view of this radiographic finding the diagnosis became clear, for here was ample cause for the recurrent attacks of cystitis. It was also clear that the coiled tube, which appeared to resemble closely a ureteric catheter, must have been introduced per urethram by the patient himself, for there had been no surgical intervention at any time.

Operative Procedure.—The bladder was opened suprapubically, and a coil of plastic tubing was removed with ease; on exploring the interior of the bladder for further foreign bodies or superadded calculi, a second and much smaller piece of plastic tubing was removed. It was noted that the bladder showed only a very mild degree of cystitis, and both pieces of tubing were as clean as if they had never been in the bladder at all, there being not the slightest signs of any phosphatic incrustations. The bladder was closed without drainage, an indwelling urethral catheter being left *in situ* for four days. The wound healed well, without suprapubic leakage of urine, and the patient was discharged home on the tenth post-operative day. The longer piece of tubing was 33 in. (83.8 cm.) in length, the shorter 5 in. (12.7 cm.). They were lengths of plastic material used to cover the wire which is employed in wireless sets and the like.

At first the patient denied all knowledge of the foreign bodies, but later stated that two years previously he had inserted an end of the tubing down his urethra (having withdrawn the inner wire). He seems to have been well pleased with his "experiment," for he inserted more and still more, until the external meatus "swallowed" the outer end before he could stop it slipping beyond his reach into the urethra. As he put it, "the tubing slipped right inside quite suddenly." He then tried to fish it out through the external meatus with the second and smaller piece, which he bent slightly to form a kind of hook. This manœuvre, however, proved to be unsatisfactory, and ended by this piece, too, slipping into the urethra and so to the bladder. After this unfortunate occurrence he remained well for approximately two weeks; then he developed symptoms of general malaise with some fever and, later, symptoms of mild cystitis. He naturally enough shrank from telling his parents, and must have spent many anxious months before finally being admitted to hospital.

Comment

It is of especial interest to note the complete absence of any phosphatic deposits on the tubing, which appeared in colour and general condition to be absolutely as new. This was in marked contrast to a large hairpin which had recently been removed from a female patient's bladder within three weeks of its insertion. In that case the hairpin was heavily incrusted with phosphates, and the bladder exhibited marked signs of cystitis: symptoms of bladder infection had started within the first week, and rapidly became quite severe.

The above case is but another example of the necessity for an *x*-ray examination of the whole of the renal tract in any case of urinary infection. It is as well to bear in mind that foreign bodies said to have been "swallowed" may in actual fact have been passed into the bladder, as was the case of the hairpin quoted above. An *x*-ray film revealed a large hairpin (confirming the patient's story that she had swallowed it) apparently lying in the region of the pelvis, and it was not until symptoms of cystitis developed and the position of the pin remained stationary on *x*-ray examinations that cystoscopy was carried out and the correct diagnosis made.

ANDREW G. BUTTERS, F.R.C.S.Ed.,
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The United States Army has ordered 1,509 dual-purpose buses, each of which can carry 37 passengers but can be converted in less than three-quarters of an hour into an ambulance accommodating 21 stretchers. Removable folding seats are fitted inside, and there are two large rear doors; otherwise the vehicle is like any long-distance motor-coach.

Reviews

THE CEREBRAL CORTEX

The Cerebral Cortex of Man. A Clinical Study of Localization of Function. By Wilder Penfield, C.M.G., M.D.(Johns Hopkins), B.Sc., and D.Sc.(Oxon), Hon. F.R.C.S.(Lond.), F.R.S., and Theodore Rasmussen, M.D. (Pp. 248; illustrated. £2 8s. 6d.) New York and London: The Macmillan Company. 1950.

No neurologists in recent years have made such extensive contributions to the study of localization of function in the human cerebral cortex as Dr. Penfield and his collaborators. They have availed themselves to a remarkable degree of the opportunities provided in the course of the surgical exposure of the brain, and in a series of papers over the last ten years they have recorded many important observations. These observations provide the main substance of the book which has now been written by Dr. Penfield and Dr. Rasmussen.

Clearly it is in relation to sensory localization that this exploration of the human brain offers the most fruitful field of study, for the human patient is able to record the nature of his own sensations and thus provide evidence not possible in animal experimentation. At the same time, the method has peculiar difficulties of its own. The conscious patient undergoing an extensive craniotomy for the removal of part of the brain is obviously not in the most favourable condition to provide accurate reports, and it may be questioned how reliable are the answers which he can give to the surgeon's questionings. In those cases reported by the authors in which a cortical lesion is combined with a definite psychosis the situation evidently presents much more serious difficulties. For this reason the reviewer feels the need for caution in accepting conclusions such as that which states that memories are "stored" in the temporal cortex. But, while it may seem desirable to urge caution in accepting some of the authors' interpretations of cortical action (which perhaps tend to be too facile), there can be no question of the value of the records they present. Without doubt they provide a most important addition to the physiology of the human cerebral cortex.

W. E. LE GROS CLARK.

THE CORONARY CIRCULATION

Coronary Circulation in Health and Disease. By Donald E. Gregg, M.S., Ph.D., M.D. (Pp. 227; illustrated. £1 11s. 6d.) London: Henry Kimpton. 1950.

Dr. Gregg's excuse for writing this monograph is that he was "inveigled into it by the urging of well-meaning friends." Of course no excuse is necessary, and we can but thank the kind friends who persuaded Dr. Gregg to undertake the task. With a humility that is so often apparent in good research workers, he offers us an exquisite critical review of this difficult and important subject.

The book opens with a short chapter giving statistical facts about the incidence of coronary disease and heart disease in general. Next comes a detailed description of the anatomy of the myocardium, the conducting system, nerve supply, coronary arteries, capillary bed, and venous drainage of the heart. There follows a helpful discourse on the technical methods that have been used as a means of studying the coronary circulation. The results of such studies are interpreted throughout with the greatest caution, possible sources of error being constantly pointed out. Findings under highly artificial experimental conditions in animals do not necessarily apply to healthy intact men. The author then discusses pressures within all parts of the coronary tree, and in another chapter describes coronary blood flow. He pays special attention to phasic changes in pressure and flow during systole and diastole. One of the most interesting sections is on the factors that govern coronary flow in health and disease and on the effects of drugs. Finally, he considers the coronary circulation in relation to clinical and experimental coronary occlusion, to cardiac hypertrophy, and to heart failure.

This dull description of the contents of the book does not do justice to the mass of reliable information given, nor to its remarkable quality. There are 637 well-chosen references, and observations proffered as facts have always been subjected to searching criticism, whether derived from the author's own work or from the literature. The book will most certainly prove a source of both comfort and inspiration to anyone interested in this field, and should appeal alike to the cardiologist, physiologist, pathologist, and anatomist. Dr. Gregg must be congratulated on producing a really interesting and much-needed treatise on a subject of great importance.

PAUL WOOD.

PEPTIC ULCER

Peptic Ulcer. By A. C. Ivy, Ph.D., M.D., D.Sc., LL.D., M. I. Grossman, Ph.D., M.D., and William H. Bachrach, Ph.D., M.D. (Pp. 1,144; illustrated. £4 16s.) London: J. and A. Churchill. 1950.

Peptic ulcer remains one of the main problems of hospital medicine, but we are still unable to translate the experimental observations into aetiological factors of clinical importance. With such an important medical problem it is necessary that all the best work should be carefully and critically brought together, and this has been done in this truly momentous book. Unfortunately there is an inverse ratio between our real knowledge of a disease and the literature relating to it, and 1,142 pages are necessary to survey the field. It is divided into four sections. Part I is an introduction to the problem of peptic ulcer. Here the authors consider basic topics such as the resistance of the mucosa of the stomach and intestine to peptic juices, and discuss in detail modern views on gastric physiology. In Part II they bring together the extensive experimental, necropsy, and clinical observations on the pathogenesis of peptic ulcer. This is the largest section of the book, covering 13 chapters devoted to specific aspects such as the experimental production of peptic ulcer, the role of the nervous system, and clinical and constitutional aspects of pathogenesis. Part III is on the problems of diagnosis, and Part IV on medical and surgical therapy in relation to physiological principles, giving a complete summary of the clinical effectiveness of the various methods of treatment. Each of the 21 chapters has a detailed summary, and each of the four main sections ends with a summarizing chapter.

The authors have contributed immensely to our knowledge of the physiology of digestion in general and to our knowledge of ulcer in particular. Throughout the book there is a splendid sense of perspective, and their own contributions are presented in relation to studies from all over the world. Many American

publications are extraordinarily deficient in references outside the U.S.A., but that criticism cannot be made against this book. The completeness of the international references, together with the clarity of presentation and admirable perspective, makes it an outstanding contribution to clinicians and to research workers, and there is no better medical use for dollars than bringing this book to British libraries. It is a monument to the inspiration of Ivy and to the industry and critical judgment of the authors, reflecting the great influence they have had in clarifying our knowledge on this modern problem.

F. AVERY JONES.

PROSTATECTOMY

Die Suprapubische Prostatektomie. By Professor Theodor Hryntschak. (Pp. 166; illustrated. M. 24.) Vienna: Wilhelm Maudrich. 1951.

Professor Hryntschak is director of the urological section of the Vienna Polyclinic, and in this volume he presents the results of an experience of prostatectomy extending over many years. The technique which he has adopted is a modification of the well-known procedure devised by S. H. Harris, of Sydney, but this he has developed on most original lines.

After a vertical incision of the abdominal wall the bladder is opened *transversely* by blunt dissection. As a result there is practically no bleeding from the vesical wall, better access is obtained to the prostatic bed, and closure of the bladder is facilitated. After enucleation of the prostate bleeding from the margins of the resulting cavity is controlled by a blanket stitch, and the margins are then brought together by one or more deep *transverse* sutures inserted with a boomerang needle-holder. The last of these sutures embraces the tip of an inserted catheter and secures its position. The bladder is most securely and effectively closed by a special form of purse-string suture which invaginates the bladder wall. The catheter is removed in 24 or 48 hours; complications are rare and suprapubic leakage is unknown.

The operative details are described with careful accuracy, and readers not familiar with German can follow them in a series of excellent drawings with legends in English. The whole volume speaks of a vast experience, and the cases which are described show results of which any surgeon might well be proud. The book deserves most careful study by every surgeon engaged in urological work. Its translation into English would be of real value.

HENRY SOUTTAR.

RECENT MEDICINE

Advances in Internal Medicine. Volume 4. Editors: William Dock, M.D., and I. Snapper, M.D. Associate editors: Tinsley R. Harrison, M.D., Chester S. Keefer, M.D., Warfield T. Longcope, M.D., and J. Murray Steele, M.D. (Pp. 549; illustrated. $10.) Chicago: Year Book Publishers, Inc. 1950.

Most of us labour under the impression that we work far harder and therefore have less time for reading than any previous generation of physicians. This impression may or may not be true, but it *is* true that there is more to read than ever before. The accelerating tempo in the progress of medicine and the vast literature which rapidly accumulates round each new discovery see to that. It is not surprising, therefore, that few of us have more than a mere nodding acquaintance with the literature on those subjects in internal medicine in which we do not happen to specialize. Such a state of affairs fully justifies this series of publications in which the literature on important advances is predigested by experts and served up in a number of well-arranged monographs each year.

This volume, the fourth on internal medicine, includes monographs on nitrogen mustards, isotopes, brucellosis, neuromuscular disorders, low-sodium diets, anticoagulants, hepatitis, hepatic tests, and hypertension. Apart from our Professor Pickering, who writes on the vascular physiology of hypertension, the authors are all Americans or Canadians. Without exception the articles are admirable—clear, critical, authoritative, and interesting. The physician who reads and digests the work can feel that he has gone a long way towards keeping himself abreast of recent advances in internal medicine. The book is beautifully produced on superb paper. It is also a superb price.

D. M. DUNLOP.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received

The Acridines. By A. Albert, D.Sc., Ph.D., B.Sc., F.R.I.C. (Pp. 381. 70s.) London: Edward Arnold. 1951.

Lecture Notes on Emergency Diagnosis without Laboratory Aid. By Professor H. L. Baur. (Pp. 68. 6s.) Oxford: Blackwell Scientific Publications. 1951.

Diathermy: The Use of High Frequency Currents. By S. L. Osborne, B.P.E., M.S., Ph.D. (Pp. 113. 21s. 6d.) Oxford: Blackwell Scientific Publications. 1950.

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MITOSIS

Cell division, and in particular nuclear division or mitosis, has been much studied in cancer research in the hopes of finding inhibitors. On March 10 (p. 496) we published a paper by H. N. Green and F. N. Ghadially in which mitotic inhibition was linked with the action of cortisone and the wider problem of surgical shock. Since the way in which chromosomes appear (prophase), arrange themselves at the equator of the spindle (metaphase) and then move to the two poles of the cell (anaphase) to form separate nuclei is becoming of medical as well as scientific importance, a survey of what is known of the physiology may be of value. It must be admitted at the outset that, apart from the plain morphological description of what is seen to happen, there is much confusion. Even the physical mechanisms responsible for the movements of the chromosomes are obscure. There have been innumerable ideas on this question (Schrader[1] lists a dozen or so of the more important ones), but there is very little agreement.

The chemistry of mitosis is in scarcely any better case, in spite of a great deal of work. We do not even know which parts of the mitotic cycle need a supply of energy, nor how this energy is provided. Many workers in the past have looked for fluctuating oxygen consumption during mitosis, but without success.[2] Recently, however, Zeuthen,[3] using very refined methods on frog and sea-urchin eggs, has found evidence of a rising consumption during and after division. But his results have been subjected to a certain amount of criticism; and as the variations are very small they leave us not much the wiser.

It is not altogether certain whether tissue-culture cells can divide in the absence of oxygen,[2] but it is well established that they are not affected by cyanide,[4] which, among other things, inhibits cytochrome oxidase. Presumably, therefore, they can obtain the energy for division from anaerobic processes or from aerobic systems other than cytochrome. On the other hand, sea-urchin eggs will not divide in the absence of oxygen, or in the presence of carbon monoxide (in the dark) or of cyanide.[5] They are also inhibited by dinitrophenol,[5] which is thought to interfere with phosphorylation, suggesting that the necessary energy is carried by high-energy phosphate compounds such as adenyl pyrophosphate. Such evidence as there is seems to indicate that no one phase of mitosis is particularly affected by these inhibitors.

Recently Bullough[6] has found that mouse cells will not enter prophase without adequate supplies of carbohydrate, though if they have started on mitosis they can complete it. He interprets this as showing that the energy for mitosis is stored up at some point before prophase, but it is difficult to be certain that he is dealing with an effect on mitosis itself rather than on the growth that necessarily precedes it.

Because of its practical importance, mitotic inhibition has been extensively studied; but from a theoretical point of view the results have been disappointing. The best known of the inhibitors is colchicine,[7] which blocks the formation of the spindle but is without effect on the chromosomes, which appear in the ordinary way; for this reason it is usually called a metaphase inhibitor. Since it is effective, at least in some cells, at dilutions as great as 10^{-6}M, there can be little doubt that it acts on the enzyme systems responsible for maintaining the particular type of orientation to be found in the spindle.

Many other substances are known which have an effect like colchicine, in particular the vast and rather ill-defined group of narcotics.[8] Their effect on mitosis, like their effect on many vital activities, is roughly proportional to their fat solubility,[9] suggesting that a lipoid phase exists somewhere in the spindle or in the enzyme systems required for maintaining it. Recent ideas about the denaturation of proteins by narcotics are perhaps relevant to this problem.[10]

Many substances act like *x* rays[11] and ultra-violet radiation[12] in causing a clumping of nuclear material (pycnosis) and in preventing cells from entering prophase. This group includes such diverse substances as urethane, hydroquinone, and various arsenical compounds; their mode of action is quite unknown.

1 *Mitosis*, 1944, New York.
2 Brachet, J., *Embryologie Chimique*, 1947, Paris.
3 *Nature, Lond.*, 1947, **160**, 577.
4 Hughes, A. F. W., *Quart. J. micr. Sci.*, 1950, **91**, 251.
5 Krahl, M. E., *Biol. Bull., Wood's Hole*, 1950, **98**, 176 (a review).
6 *J. Endocrinol.*, 1950, **6**, 340.
7 Eigsti, O. J., *Lloydia*, 1947, **10**, 65 (bibliography).
8 Levan, A., and Ostergren, G., *Hereditas*, 1943, **29**, 496.
9 Ostergren, G., ibid., 1944, **30**, 429.
10 McElroy, W. D., *Quart. Rev. Biol.*, 1947, **22**, 25 (a review).
11 Lea, D. E., *Actions of Radiations on Living Cells*, 1946, Cambridge.
12 Giese, A. C., *Quart. Rev. Biol.*, 1947, **22**, 253 (a review).
13 *Nature, Lond.*, 1947, **159**, 794.
14 Loveless, A., and Revell, S., ibid., 1949, **164**, 938.
15 Wilson, E. B., *The Cell in Development and Heredity*, 1925, New York.
16 Faure-Fremiet, E., *La Cinétique du Développement*, 1925, Paris.
17 Auerbach, C., and Robson, J. M., *Proc. roy. Soc. Edinb., B.*, 1947, **62**, 271.
18 Loveless, A., *Nature, Lond.*, 1951, **167**, 339.
19 Fischer, A., *The Biology of Tissue Cells*, 1946, Cambridge.
20 Heilbrunn, L. V., *An Outline of General Physiology*, 1943, Philadelphia.
21 Burrows, H., *Biological Actions of Sex Hormones*, 1949, Cambridge.
22 Tyler, A., *Physiol. Rev.*, 1948, **28**, 180 (a review).
23 Runnstrom, J., *Adv. Enzymol.*, 1949, **9**, 241 (a review).
24 Wigglesworth, V. B., *The Principles of Insect Physiology*, 1950, London.
25 Quetel, R., *Rev. gen. de bot.*, 1939, **51** (several review papers).

Dustin[13] has drawn attention to the existence of these two essentially different types of mitotic inhibition, and classifies mitotic poisons by whether they block at metaphase, or whether they prevent cells from entering prophase (pre-prophase inhibitors). Because of the similarity in effect between the latter group and radiations, he refers to them as "radiomimetic," though others prefer to reserve this term for substances which produce inherited chromosome abnormalities.[14] Many substances can apparently produce either type of inhibition, depending on when they are applied; nevertheless Dustin's classification probably reflects something of the fundamental mechanism underlying mitosis. It may be significant that only two stages of the mitotic cycle are ever observed to be normally greatly prolonged. One of these stages is of course interphase, in which the majority of cells spend all their time. But many invertebrate eggs are shed in the metaphase of one of the maturation divisions,[15] and remain indefinitely in this state unless they are fertilized. Prophase and anaphase, on the other hand, almost always go through without interruption. The implication of this would seem to be that mitosis is either controlled by two master processes, one involved in prophase and the other in anaphase, or by a single process which reverses at metaphase. The cycle of changes in the chromosomes and in the physical properties of the cytoplasm and the cell surface[16] seem to demand some such mechanism.

Loveless and Revell[14] have put forward a rather different classification of mitotic poisons. Though they recognize Dustin's two categories, they attach much greater importance to what they call the truly radiomimetic substances—that is, substances which produce inheritable chromosome abnormalities. Foremost of such compounds are the nitrogen-mustards, which cause breaks, anaphase bridges, and other changes. They also produce mutations.[17] Their activity is apparently due to the fact that they give rise to two carbonium ions,[18] and Loveless and Revell think that they produce their effects by cross-linking protein or nucleic acid molecules, though it is questionable whether such a mechanism is sufficiently specific. This scheme of classification perhaps lays an undue stress on changes in the chromosomes, to the exclusion of events in the spindle and cytoplasm, but it has the merit of emphasizing the importance of the ultimate genetical control of the whole process.

Yet another category of mitotic inhibition is recognized by Hughes,[4] who finds that various substances block the reconstruction of the nucleus in telophase. The significance of this is obscure.

Though the situation with regard to mitotic inhibitors may be confused, the question of the stimulus to mitotis is worse confounded. A particular difficulty is to disentangle the effects of substances on cell growth from the effects on cell division. Since most cells maintain a more or less constant size, it is generally held that after a division there must be growth in order to restore the conditions for a fresh division. The fact, therefore, that divisions can be elicited by supplying various substances may not mean that they are stimulating mitosis, but simply that they are essential growth factors. A great deal of work has been done on this problem, using mainly tissue cultures. From time to time breakdown products of proteins, as well as complex nucleoproteins, have been supposed to be the essential stimulus,[19] but in no case has it been shown convincingly that these substances are needed for mitosis rather than growth.

There is a considerable body of evidence that substances released by damaged cells have an effect in stimulating division—as, for instance, in wounds.[20] It appears also that dividing cells have some influence in stimulating others to division, since in testes and in the anthers of plants whole blocks of cells can be found in identical stages. Sex hormones too have a stimulating effect on many tissues.[21] In none of these cases, however, has it so far been possible to separate the effects on growth and mitosis. In fact, it has often been supposed that there is no specific stimulus to mitosis, and that, given all the requisites for growth, mitosis follows automatically. The fact that many cells do not divide would then be due to the presence of mitotic inhibitors or to the absence of essential growth substances.

So complicated is this question of separating growth and mitosis that there is much to be said for studying the stimulus to division in cells where all the substances needed for growth are known to be present. This is the case, for instance, in most eggs, where the stimulus or the removal of the inhibition is effected either by fertilization or by artificial activation.[22 23] Some interesting parallels between this and other types of biological stimulation have been discussed by Heilbrunn,[20] who maintains that the changes in question seem to be associated with the release of calcium into the cell. But this may be a secondary effect rather than a primary cause.

Long periods of dormancy are found in insect embryos[24] and in plant seeds,[25] where all the requirements for growth seem to be present. Mitosis can, however, be started up by various forms of shock, though very little is known of the mechanisms involved.

It is easy to be disheartened at the fragmentariness of our understanding of mitosis. Great advances, however, have never come from a preoccupation with diversity, and even now, no doubt, the clues for a synthesis are in existence. But they are not likely all to be concentrated in one corner. No activity of the cell involves so many aspects of structure and function as mitosis, and no attempt at trying to understand it is so likely to succeed as one that takes all these aspects into account.

CLOSED SHOP IN DURHAM

In the autumn of last year Durham County Council threw down a challenge to the medical and teaching professions by insisting that trade union membership should be obligatory on those doctors and teachers employed by it. It appeared that the council would accept membership of the B.M.A. as being sufficient for this purpose. The reaction of the B.M.A. and the National Union of Teachers was prompt and unambiguous. Neither organization was prepared to accept the idea that membership of a union or other appropriate body should be a qualification for professional employment under a local authority. Following a letter from the Secretary of the B.M.A., the Chairman of the Public Health Committee, Dr. Metcalfe Brown, and Dr. E. Grey Turner, Assistant Secretary of the B.M.A., addressed a meeting of medical officers in Durham, at which they received the fullest support from those concerned in carrying out the Association's policy.[1] At the same time both the Minister of Health and the Minister of Education, while admitting that they thought it desirable that employees should be members of the appropriate trade unions, deplored the county council's action in seeking to make this obligatory. Mr. Tomlinson, the Minister of Education, for example, said that he could "not remain indifferent to this threat to the educational service, and if need be I should use the powers which the Act gives me to prevent it." It is not clear whether as a result of this the Durham Council disavowed its policy, but, at all events, it seemed prepared to adopt Brer Rabbit's policy of lying low and saying nothing—for the time being. Last week it was obvious that it had no intention of doing nothing, but was determined to achieve the same end by the apparently innocuous method of asking intending candidates for posts whether or not they belonged to a trade union. The National Union of Teachers thereupon decided to call for the resignation of those teachers employed by the Durham County Council if it continued to apply this policy. The Minister of Education, as a result, directed the council to refrain from taking any steps to ascertain whether applicants for teaching posts were or intended to become members of a trade union or other appropriate body. A meeting of delegates of the twenty-three local associations of the National Union of Teachers, on April 7, backed up the Minister's intervention and gave full support for "whatever action may be necessary to secure the principles enunciated by the general secretary of the N.U.T." An attempt was then made to bring pressure to bear in the opposite direction through a meeting of the Durham County Federation of Labour Parties, but fortunately this meeting did not give the Durham Council the support it had hoped for. As commentators in the press have pointed out, this is a case in which the employer has been seeking to enforce the closed shop policy, and not the employees through their unions or professional organizations.

It is yet to be seen whether the Durham County Council will, undeterred by the present controversy, seek to find out from future medical applicants for posts under its authority whether they belong or intend to belong to a trade union or other appropriate professional organization. The B.M.A. will certainly be as vigilant on behalf of doctors who apply for posts in Durham as has the N.U.T. been on behalf of teachers, and it will quickly learn whether such doctors are being asked this question and as quickly support them in their refusal to answer it. The last local authority which sought to impose trade union membership upon its medical employees was Willesden, when its local council, in December, 1946, served notices of dismissal on nurses and doctors in two of its hospitals who refused to comply with this condition of employment. When the matter became public, Willesden had to retreat from its morally untenable position. The medical profession must determine to defeat a repetition of this if the Durham County Council tries to enforce its policy in any way, however indirect. It is heartening, in these days of regimentation, to see the two great professions of medicine and teaching insist upon opposing these local attacks against freedom of conscience. Once one authority has succeeded in making a breach in professional freedom in this way, it would be so much the easier for other authorities to follow suit and so much more difficult for professional organizations to make effective opposition.

[1] See leading article, *British Medical Journal*, 1950, 2, 1210.

GANGLION-BLOCKING AGENTS

The growth process of modern therapeutics resembles the ebb and flow of the tide, and in the two papers on ganglion-blocking agents published this week both the ebb and the flow are illustrated. Dr. W. D. M. Paton has written a valuable review, clearly explaining in a cautious and yet hopeful manner the peculiar properties of the different substances which paralyse ganglia: his account is suffused with the optimism which should mark the laboratory worker. But Drs. S. Locket, P. G. Swann, and W. S. M. Grieve describe an investigation which pours cold water on the use of these substances in the treatment of hypertension. They have not failed in the clinician's duty to be objective in assessing their results.

One of the points of special interest in Dr. Paton's review is his suggestion that ganglion-blocking agents may be more effective when the ganglia are transmitting more impulses than normally. When the preganglionic fibres to the superior cervical ganglion are stimulated continuously the effect of hexamethonium becomes greater the longer the stimulation is continued. This, he thinks, may be the reason that doses which reduce hypertension or relieve the pain of gastric ulcer do so without paralysing the small intestine and the bladder. The ganglia which transmit more impulses than normal are paralysed by doses which are ineffective on other ganglia. Another suggestion concerns the postural hypotension which develops in patients given hexamethonium. The fall of blood pressure caused by the intramuscular injection of hexamethonium lasts for periods which rarely exceed two hours. At the end of this time the blood pressure is restored. If, however, the patient stands up he may faint because of a fall of blood pressure which then occurs. The hypotension is promptly remedied by exercise, and Dr. Paton suggests that it may be caused by a pooling of blood in the veins, in which the tone is recovered more slowly than in the arteries. The loss of venomotor tone is, however, counteracted by the increase in venous return which muscular work induces. Very little attention is given at the present time to venomotor tone, though there is evidence of its importance. Perhaps it can be studied by the use of ganglion-blocking agents, though it is difficult to imagine how the duration of their effect on ganglia supplying fibres to the arteries and on those supplying them to the veins can differ.

The clinical results described by Drs. Locket, Swann, and Grieve appear to conflict to some extent with the results of earlier workers to whom they refer in their paper. But this is not very surprising. It has always seemed unlikely that a substance which has an action of relatively short duration, such as one to two hours, can be profitably used to maintain normal blood pressure throughout the day. The last word in this matter has probably not yet been said. It may be that, as Dr. Locket and his colleagues appear to suggest, the good results which have been reported are due to rest in bed and to the use of the bromide salt of the methonium compounds. Time will show. In the meantime we are all learning much more about ganglia than we knew before.

PROGNOSIS AFTER STREPTOMYCIN THERAPY

Though streptomycin is a curative weapon of vast potentialities the occurrence of relapses, including long-delayed relapses, during or after treatment of tuberculous infections has had the effect of restraining optimism about the likelihood of complete cure. Now that observations based on follow-up surveys are becoming available, a more reliable assessment of the long-term results of streptomycin therapy is possible. A report[1] submitted to the Medical Research Council gave the results of treatment with streptomycin of acute miliary tuberculosis in 25 patients, of whom 19 were aged less than 15 years. The 14 survivors have been followed for over two and a half years. In the U.S.A. Bunn[2] has continued to observe the survivors out of a series of 100 adult patients given streptomycin for acute miliary infection, meningeal infection, or a combination of both. Twenty-one of these 100 patients were alive 19 to 28 months after completion of treatment. Though the two series differed widely in clinical material they both provide additional evidence that in experienced hands streptomycin offers prospects of healthy survival in some 50% of miliary tuberculous infections. What are the factors which determine response to treatment? Available evidence suggests that prognosis is most serious when the clinical state at the onset of treatment is acute and when response to early treatment is sluggish. A threat of complicating meningitis always exists and may materialize at any time, either during treatment of the miliary infection or after treatment has been stopped. The need is to be constantly on the alert for the earliest evidence of meningeal infection. With this object British and American workers are agreed in advocating early and repeated examination of the cerebrospinal fluid in all cases of miliary tuberculosis.

Meningitis complicating miliary infection necessarily makes for a grave prognosis, but a fatal result is no longer inevitable. Age is an important factor. The conclusions reached by the Ministry of Health[3] about the streptomycin treatment of tuberculous meningitis are undoubtedly encouraging. It is to be hoped that the results which have prompted the conclusions will be published in greater detail, more especially in so far

[1] *Lancet*, 1950 **1**, 841.
[2] *Amer. J. med. Sci.*, 1948, **216**, 286.
[3] *British Medical Journal*, 1950, **2**, 413.
[4] Ibid., 1949, **1**, 338.
[5] Ibid., 1950, **2**, 1073.

as they apply to children of different age groups. Elsewhere in this issue Drs. W. L. Calnan, J. Rubie, and A. F. Mohun take a stage further a follow-up study of 54 cases of tuberculous meningitis treated with streptomycin. The minimum period of observation is now two and a half years. Two more of the patients have died since the last report,[4] but 16 of the 54 (30%) are still alive. Three children had relapses respectively eight, three, and four months after they had apparently fully recovered, but they were again successfully treated with streptomycin. The Ministry of Health suggests that there is, among practitioners, incomplete appreciation of the value of streptomycin treatment. But surely the practitioner does not lack appreciation: what he does not as yet possess is confidence in streptomycin comparable with that which he has in, for example, sulphonamide or penicillin therapy. To some extent this is understandable. While there can be no denying the altogether remarkable progress achieved with the help of streptomycin, the fact is that in some respects treatment remains empirical. The problem presented by the creation of streptomycin-resistant strains remains unsolved. In another paper in this issue Drs. Calnan, Rubie, and Mohun report on the ineffectiveness of intrathecal injections of sulphetrone when added to the streptomycin treatment of tuberculous meningitis. The trials with adjuvant forms of therapy are tacit admission of the fact that streptomycin has its limitations, though the Medical Research Council's report[5] on the combined use of streptomycin and P.A.S. in pulmonary tuberculosis was distinctly encouraging.

The chances of relapse, complications, or sudden death during streptomycin treatment cannot be foretold or even suspected with any real reliability. In encouraging the relatives to agree to treatment of a patient the family doctor knows that he is submitting the family, no less than the patient, to a lengthy period of strain and uncertainty, with no assurance about the ultimate result. The immediate task of the practitioner in the household and at the bedside will be eased as the results of research provide surer grounds for assessing prognosis. Meanwhile it cannot be ignored that advances in therapeutics, no less than changes in the patterns of disease, give rise to new and human problems.

N.H.S. ON THE AIR

The discussion on the N.H.S. arranged by the B.B.C. on the Home Service last week was, like all such B.B.C. talks, useful more because it will set people thinking than for any fresh light it threw on the problem. It was interesting, too, because much of what was said probably reflected faithfully the reactions of many people both inside and outside the profession to a service which is costing the country between £400m. and £500m. a year; or, as one speaker put it, is costing 9 guineas a person a year, towards which only 16s. 6d. comes from the National Insurance fund.

Nearly all talks and conversations about the Health Service begin with remarks about the size of the national drug bill, and in this the B.B.C. was true to pattern. The "man in the street" started off by referring to the expensive prescription given to a little girl with whooping-cough, asking the question whether the price was justifiable. Someone immediately added that the new antibiotics were very expensive, and another said that the manufacturing chemists were "expert in sales propaganda and wearing down the doctors' resistance." Someone else came in with what many people would now regard as a naïve rejoinder—that the only way of saving money on drugs would be to nationalize the pharmaceutical industry. Much more might have been made of the enormous contribution the pharmaceutical industry has made and is making to research, and also of the risks it is prepared to bear in manufacturing a new product—the production of penicillin in America during the war was an outstanding example of this. A general practitioner observed that thanks to penicillin and the sulphonamides many cases of pneumonia need no longer be sent to hospital for treatment, adding that the new remedies saved lives but cost money. But, here again, the thinking might have been carried a little further. The new remedies which make it unnecessary to send patients with pneumonia to hospital more than pay for themselves by saving hospital costs and by shortening the duration of illness and, so, the time the patient is absent from work.

This question of the cost of new drugs is only part of the problem represented by the "bottle of medicine." The "bottle of medicine" is, so to say, a hangover from the days when efficacious drugs were few and far between. When there were few drugs that could do any good there was always the hope that any drug might do some good. The prescription and the "bottle of medicine" became the symbol of the medicine man's magic. Now that medicinal therapeutics are on a more rational basis it should be possible gradually to wean the patient from his favourite brightly coloured medicine—but it will have to be gradual.

The next theme of the B.B.C. talk was the general practitioner and his conditions of work. First, the point was made that general practitioners are overworked, and this largely because of the great increase in the numbers attending the surgery. The talk then went on to group practice and health centres, someone observing that it was a waste of time to build health centres, because "for every one built there would be a hundred new houses the fewer." Co-operation of general practitioners through group practice was an idea which received strong support.

If the discussion seemed to flag a bit on the above themes, it certainly warmed up when the turn of the hospitals came. Clumsy administration and extravagant expenditure were two faults levelled at the hospitals under the N.H.S. As one speaker put it, we were suffering from the fact that responsibility for management was separate from responsibility for function. The regional boards and management committees were not given real financial responsibility. There was no incentive to save, as no region was allowed to carry over the saving from one financial year to the next. "The policy is being centralized, because policy goes with money; it always does. If you have pay from Whitehall you

have control from Whitehall." Voices were raised in favour of the block budget, and it was suggested that if, after trial, this did not succeed the choice would remain between direct management by the Civil Service (" which I think would be a disaster "), or by the local authorities. One speaker pleading for the block grant said that if the Government could trust the B.B.C. and the University Grants Committee, why could it not trust the regional hospitals boards in the same way? This was followed by the observation that " all political parties confront the present out-of-date structure of local government, and we centralize our services instead of reforming our local government." Later on the view was put forward that there should be a unification of the three parts of the N.H.S.; under reformed local authorities—" reformed as to area and functions, and planned to create 40 or 50 new authorities." This seems to be a return to the Willink plan of joint authorities.

Interesting as it was, the B.B.C. talk on the N.H.S. suffered from ranging too diffusely over too big a field. Any one of the three main themes touched on would be subject enough for a discussion to itself. A further talk, for example, on the finance and administration of the hospital service should be of great interest and value.

ORF

Recent letters in this *Journal*[1-5] have again drawn attention to the occurrence in human beings of a skin eruption due to contagious pustular dermatitis (C.P.D.) of sheep (orf). Elsewhere in this issue Dr. I. S. Hodgson-Jones describes eight cases seen in a London hospital. In 1928 Glover,[6] working at Cambridge with Berkefeld V filtrates of scrapings from infected animals, showed that it was possible to transfer the infection to normal lambs, and in 1934 Newsom and Cross[7] transmitted the infection from an infected human to a sheep, but the nature of the virus was not studied. Though veterinary surgeons had long realized that contagious pustular dermatitis of sheep could affect man,[8 9] and Hatziolos[10] in 1929 had written a thesis on " L'Ecthyma Contagieux du Mouton," the first report to appear in dermatological literature was that of Peterkin,[11] who described five of the cases he had seen in Edinburgh. He failed to transmit the infection to a human volunteer because he used a Berkefeld N filter, through which this virus cannot pass. Later Schoch[12] and Nomland[13] described cases in the U.S.A., and in 1948 Blakemore and his colleagues[14] isolated from a human case a virus morphologically and immunologically identical with a strain of C.P.D. (Glover's U.F.). The disease was transmitted to a human volunteer, and scabs removed from his skin proved infective to a lamb.

In sheep the eruption tends to vary in different parts of the country. In the south of England foot lesions are rare, while in the Scottish border country the feet are affected chiefly in July and August and the mouths of young lambs in spring. In the north-east of Scotland there occurs a form of dermatitis of the legs of sheep called " strawberry foot rot," which is transmissible to man and in which the clinical and histological picture closely resembles contagious pustular dermatitis.[15] There is evidence[16 17] that the infective agent of S.F.R. differs from that of C.P.D.

The number of humans infected depends on the density of the sheep population in the area. Thus a comparatively large number of cases are seen in sheep-rearing regions such as the lowlands of Scotland, the north of England, East Anglia, and Australia. The clinical appearance of the disease is quite characteristic and readily diagnosed by many country doctors, but, as Dr. Hodgson- Jones shows, the conditien may be seen in urban practice among butchers, slaughterhouse workers, and even housewives. All his eight patients had handled sheeps' heads from the Scottish lowlands. The initial lesion is a dusky-red papule, which soon grows to the size of a sixpence or half-a-crown, and is firm and painless. It resembles a huge molluscum contagiosum or the " molluscum " type of squamous-cell carcinoma, but the depressed centre is covered by a white membrane, which, if incised, exudes a serous exudate. The tumour is often diagnosed as a carbuncle or abscess, and once the membrane has been ruptured secondary sepsis occurs and it assumes the appearance and characteristics of a granuloma pyogenicum. As a rule lymphadenitis and adenitis do not occur unless secondary infection is present. The lesions are usually solitary, but occasionally multiple " orf " tumours are seen, while, rarely, an eruption closely resembling erythema multiforme develops. Orf requires no specific treatment, though it is usually wise to prescribe mild antiseptic wet dressings, such as 5% ichthyol or boric acid, to prevent septic infection.

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5 Peterkin, G. A. G., ibid., 1951, **1**, 588.
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7 *J. Amer. vet. med. Ass.*, 1934, **84**, 799.
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THE BUDGET AND THE N.H.S.

In his Budget speech Mr. Hugh Gaitskell said they had decided to bring the Health Service estimates within a total of £400m. This for the time being would have to be a ceiling. The only way to keep within this limit would be to find some other source of revenue. The Government had therefore decided to introduce a charge for some dental work and optical services—about half the scale fee for all denture work and about half the cost of each pair of glasses. There would be no charge for children's glasses. Expectant and nursing mothers would continue to receive dental treatment, including dentures, from the local authority service. Such a charge has been advocated several times in these columns. A leading article in *The Times* suggested that this principle might be extended to other goods provided by the Service.

REFRESHER COURSE FOR GENERAL PRACTITIONERS

DRUG ERUPTIONS

BY

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The term "drug eruption," or dermatitis medicamentosa, refers to any eruption attributable to the action of a drug which reaches the skin by way of the blood stream, irrespective of the method by which it has been administered. The term does not apply to any local reaction which may occur as a result of direct contact of the drug with the skin from the outside, but it does include eruptions attributable to drugs which have been absorbed through the skin into the blood stream, whether or not this process is accompanied by a local reaction at the point of entrance.

Introduction

Drug eruptions present the most varied clinical manifestations, and all the primary skin lesions—erythema, papules, bullae, etc.—may result from drug action. These lesions can be regarded as being primarily vascular in origin. Some are merely transient neurovascular reactions, while in others the inflammatory process may be associated with structural changes in the skin which, depending on their degree, may be of long duration. A true eczema reaction is seldom seen in dermatitis medicamentosa even though a large number of drugs can produce it in susceptible individuals when brought into external contact with the skin. In a few instances a visible change may be caused when the drug is deposited in the skin, but such examples of cutaneous drug action cannot be classed as eruptions, and the same may be said of the alterations in epidermal growth produced by drugs such as arsenic.

The characteristic lesion of an eruption due to a given drug may be totally different in one individual from that in another. Factors intimately connected with the reacting tissue must therefore operate in determining the nature of the response. There are thus two types of individual variation in response to drugs; one involving susceptibility to the pharmacological action, and the other the variation in the incidence of untoward phenomena including skin eruptions, and so far as is known there is no correlating link between these two variables.

As the capacity of the skin to vary its reactions to noxious agents is limited, the lesions presented by drug eruptions are similar to those seen in other skin diseases due to infections and intoxications or of unknown origin. In drug eruptions the disposition of the lesions with regard to each other, their course, and their duration differ in detail from that seen in other forms of skin disease. In spite of this there is not infrequently a close similarity between drug eruptions and other dermatoses, and differential diagnosis may at times be difficult. It is possible that some of the eruptions which appear during the administration of a drug are due not to the direct effect of the drug on the skin but to the action of some toxin which has been liberated from the site of the disease under treatment or from some latent focus of infection. This mechanism is referred to as biotropism, and it would account for the close similarity between some eruptions attributed to drugs and those due to infections—for example, the erythema nodosum reactions.

Drug eruptions have the following peculiarities with regard to their mode of production. As already emphasized, they are unusual effects of drug action and, even in the type associated with prolonged structural alteration of the tissue, the threshold dose may be minute. So far as is known, and with the exception of phenylethylhydantoin, it is not possible to produce drug eruptions at will. In the case of inorganic arsenic there is, however, some relation between cumulative dosage and alteration in skin growth. The individual susceptibility to develop an eruption is usually specific for a given drug or chemical group, it is seldom polyvalent, and it is never a universal cutaneous hypersensitivity in which the skin reacts to all drugs. Drug eruptions therefore possess some of the characteristics attributed to allergic phenomena, but, as some of the criteria of allergy are lacking, it might be more appropriate to call them idiosyncratic rather than allergic. For instance, it is not possible to demonstrate by means of scratch or intradermal tests a capacity to react after injection or parenteral administration, and no antibodies can be demonstrated in the blood by passive transfer experiments. That the factors immediately responsible for the cutaneous response are localized in the skin would appear to have been proved by grafting experiments in fixed drug eruptions.

With therapeutic doses the possibility of producing an eruption seems to vary with the type of drug. The frequency and comparative incidence of eruptions due to different drugs must, however, depend to some extent on the size of the population to which the respective drugs are administered. For instance, eruptions due to phenobarbitone are often seen, while those due to digitalis are rare, but the number of people who ingest these drugs is very different, and the percentage incidence of eruptions due to phenobarbitone is probably low. In the case of the organic arsenicals and gold, which are administered only to a small percentage of the population and which are notorious producers of skin eruptions, repeated administration may even appear to induce cutaneous hypersensitivity, though this could be explained on the assumption that the drug must accumulate to a critical concentration in the cutaneous tissue before a reaction develops.

General Characteristics

Drug eruptions present general characteristics which should lead to their presence being suspected. They are for the most part extensive and symmetrical in distribution; they are usually of short duration, disappearing almost immediately the drug is withheld; and the degree of itching associated with them is variable, complete absence of itching often being observed. There are, however, notable exceptions to these common

findings. For instance, the eruption due to a heavy metal may persist for many months after the drug has been discontinued. With other drugs, the eruption may be limited to a restricted area where recurrence takes place with any subsequent administration.

Drug eruptions are seldom associated with general symptoms, but on occasion they may be accompanied by fever, collapse, blood changes, and asthma, all of which can be regarded as idiosyncratic responses comparable in nature to the eruption itself. In rare instances a grave systemic upset in association with skin manifestations may prove fatal—for example, with organic arsenical preparations.

It is not possible to give a comprehensive list of drugs which have been reported as having caused eruptions; it would be more appropriate to state that, with the exception of vitamin preparations and normal saline, the administration of any medicinal substance may produce skin lesions. The same types of eruption are seen today with new drugs as were noted fifty years ago with drugs now seldom if ever used, such as copaiba and cubebs; on the other hand, new drugs have been found to cause eruptions of a type and course not previously described.

While a large number of common drugs produce eruptions which are identical in appearance and which have no distinguishing feature to suggest that this or that drug is the cause, the eruptions produced by a small number of drugs present features which permit a fairly accurate guess to be made of the actual drug which has caused them. Such drugs usually produce skin lesions other than simple erythema. These tend to have an unusual distribution; sometimes they pursue a prolonged course after cessation of the drug and present some similarity to classified skin diseases not due to drugs. Distinctive eruptions of this type due to drugs at present in common use merit detailed consideration.

Distinctive Eruptions

Phenobarbitone.—Eruptions caused by this drug usually take the form of a transient itchy morbilliform or punctate erythema. Occasionally, however, a severe generalized eruption develops, beginning as an erythema-multiforme-like rash affecting the limbs and mouth and proceeding to a generalized scarlatiniform erythema sometimes associated with superficial subcorneal bullae. This eruption may persist for a few weeks and may be associated with considerable constitutional disturbance (Fig. 1).

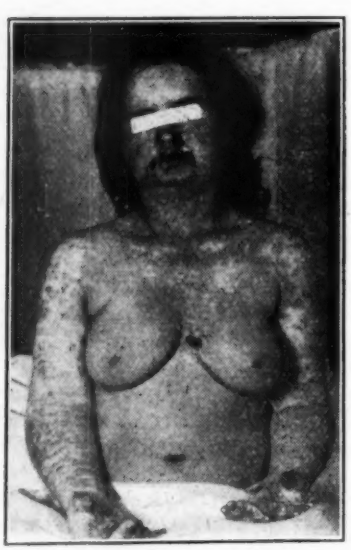


FIG. 1.—Severe generalized erythema, with mucous membrane involvement, due to phenobarbitone.

Opium and its Derivatives. — An urticarial eruption is often caused by such preparations. It differs from ordinary urticaria in the persistence of the weals and the absence of the usual periodic freedom from lesions. The weals are associated with brilliant or dusky surrounding erythemata to a much greater extent than is usually found in ordinary urticaria, and they may be almost entirely free from itching. Apart from their administration for their analgesic effects these substances occasionally cause a rash of this type when used in cough mixtures and antipyretic mixtures.

The Sulphonamide Group.—These preparations when administered by mouth may produce scarlatiniform, morbilliform, purpuric, erythema-multiforme-like or bullous eruptions (Fig. 2). In some cases the rash may persist for a number of weeks and be associated with fever.

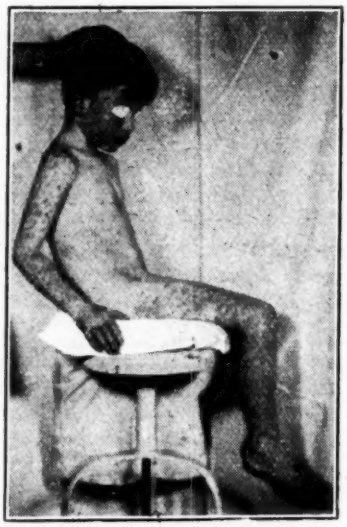


FIG. 2.—Erythema multiforme-like eruption due to a sulphonamide.

Erythema nodosum lesions sometimes develop during administration of these drugs and they may be indistinguishable from those associated with tuberculosis and other infections.

Sulphonamides may give rise to hypersensitivity to sunlight, and while this may occur as a result of oral administration it is much more likely to develop if the drug has been absorbed through a skin lesion or from a wound. In the latter case direct contact with the skin will take place almost inevitably, and it would seem that photosensitivity develops to a much higher degree when there is a combination of cutaneous contact with concomitant or subsequent absorption. The development of photosensitivity is attested by the sudden appearance of an acute eczematous dermatitis on uncovered areas within a few hours of exposure to sunlight.

These effects of the sulphonamides on the skin are produced by varying amounts of the drug, and while the manifestations attributable to the sulphonamide alone are transient the state of photosensitivity produced by it may persist for at least two years, and in rare cases the areas repeatedly affected by sunlight may become atrophic and resemble in appearance an *x*-ray atrophy with telangiectasia and pigmentation. For this reason, and quite apart from the fact that a contact eczema may also be produced, the use of sulphonamide preparations as local applications to the skin should be avoided. These preparations may also cause eruptions of the fixed type.

Gold Salts, Organic Arsenical Preparations, and Metallic Mercury.—These may all produce a severe generalized simple dermatitis (non-eczematous) which lasts for months after their administration has been stopped. The eruption may develop after one or several therapeutic doses, or following a course of treatment which seems to have been well tolerated initially. The first cutaneous manifestations may be apparently insignificant localized patches of scaly erythema which later become generalized, or the entire body surface may become suddenly erythematous associated with swelling of the face and extremities. As a

result of cutaneous oedema superficial bullae may develop under the stratum corneum, and when these rupture a persistent weeping surface is produced. After a short time exudation becomes negligible and a state of dry scaly erythroderma gradually becomes established, characterized by more or less leathery thickening of the skin and scaling.

In the case of gold salts this hypertrophic process progresses to the formation of circumscribed plaques, or large areas, closely studded with small hard nodules and papules which bear a striking resemblance to those of lichen planus both in contour and in colour (Fig. 3). As time passes the melanogenic function of the skin becomes extremely active, so that deep brownish pigmentation is superadded to the erythroderma. This capacity to stimulate cutaneous pigment formation is common to all the heavy metals. As the eruption persists the hair falls out. With all three drugs intense itching accompanies the eruption, and in the early stages there may be fever, constitutional upset, prostration, and evidence of damage to the liver and kidneys. Although gold, organic arsenic, and prolonged mercurial therapy is given to comparatively few the incidence of skin manifestations is high and must be constantly watched for, as they are often the most severe and dangerous of all drug eruptions. At the first sign of an erythema the drug must be stopped.

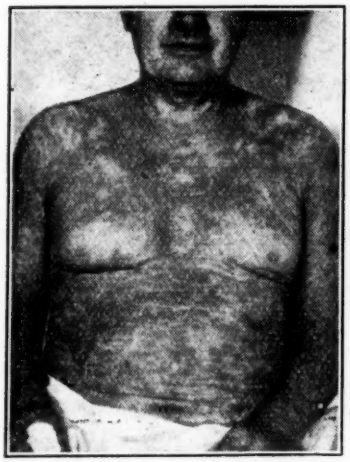


FIG. 3.—Lichenoid eruption due to gold, six months' duration.

In contrast to metallic mercury and inorganic mercurial preparations the recently introduced mercurial diuretics, even when administered for long periods, seldom produce skin rashes, and when they do so the eruption is a non-characteristic erythema which quickly subsides on cessation of the drug.

The cutaneous manifestations due to inorganic arsenic are totally different from those caused by the organic preparations. Oedema of the conjunctiva may occur after small amounts of inorganic arsenic or after prolonged ingestion. Melanin pigmentation of exposed areas and pressure points and further darkening of areas already pigmented occur. In skin diseases treated with arsenic residual pigmentation of the lesions is a frequent and annoying feature. Gross hyperkeratosis of the palms and soles may develop. Localized keratoses and cutaneous horns, both of which may become carcinomatous, may appear on exposed areas, the action of light seeming to play a part in this process. Prolonged erythroderma such as is produced by organic compounds is not seen with inorganic arsenic.

Iodides and Bromides.—The eruptions produced by these drugs are almost identical, and apart from the macular erythema and purpuric types they are characteristic. The commonest is probably a deep-seated papular eruption affecting the face and often the trunk and limbs as well. The papules become necrotic in the centre, thus resembling pustules, and the eruption is described as acneiform. The lesions are not necessarily situated at follicle mouths, are not associated with comedones, and of course the eruption is not limited to the period of puberty. Apart from these considerations the lesions are more solid, more deeply seated, and larger than ordinary acne lesions and in fact may be so nodular in character as to suggest a syphilide. Another type of nodular eruption which may develop on a circumscribed area, in the region of the nose, elsewhere on the face, on the limbs, or the trunk, consists of a nodule, or group of nodules which coalesce, and which enlarges to tumour size, ulcerates, and fungates. These nodular manifestations of iodide or bromide intolerance persist for a long period after cessation of therapy, as they are produced by a massive granulomatous type of infiltrate which will obviously require some time to dissolve. Iodides may cause an eruption resembling erythema nodosum. Both drugs, but more especially iodides, may give rise to a persistent bullous eruption resembling dermatitis herpetiformis (Fig. 4), and the administration of iodides to cases of true dermatitis herpetiformis may cause an exacerbation of the lesions in some cases. All of these eruptions may be accompanied by fever and prostration, and may prove fatal.

FIG. 4.—Bullous eruption due to iodide.

The Antibiotics. — Penicillin, streptomycin, and "aureomycin" are all capable of causing skin eruptions, and it would seem that streptomycin does so more often and aureomycin less often than penicillin. The rashes take the form of widespread urticarial lesions, erythema, or erythema-multiforme-like lesions, all of which appear during the first ten days of a course or after a single injection. There may or may not be a reaction at the site of injection. The eruption may be accompanied by fever and swelling of the joints and tendon sheaths. These manifestations persist for days, and may recur after a period of quiescence even though the drug has not been readministered. In the case of penicillin it has been noted that the presence of cutaneous fungus infections seems to increase the possibility of a skin eruption and such infections may themselves be aggravated by its administration. The drug reaction may take the form of cheiropompholyx, and it is possible that the latter may in fact be due to absorption from an existing fungus lesion which has been activated by the penicillin. It has been suggested that the penicillin eruptions may be true allergies, the tissues having been previously sensitized by contact with moulds encountered naturally. Impurities in the penicillin are undoubtedly the irritants in some cases. Erythema has been noted during chloramphenicol administration.

It has been found possible to desensitize to penicillin by administering it orally, and that eruptions due or attributed to streptomycin may disappear in spite of the administration of the drug being continued.

Some of the antibiotics, notably aureomycin and chloramphenicol, cause glossitis and cheilitis. These are due to a profuse growth of monilia. In ordinary circumstances the growth of these organisms is inhibited by the normal bacterial flora of the mucous membrane. The antibiotics, by reducing or abolishing the growth of these bacteria, permit the growth of monilia to proceed unchecked. Interference with the absorption and metabolism of vitamin B, owing to interference with the natural flora of the gut, has also been suggested as the cause of the mucous membrane lesions, but their onset is too rapid to be explained on the basis of a vitamin deficiency.

Phenytoin and Methoin.—These recently introduced anticonvulsant drugs for the treatment of epilepsy seem to produce morbilliform erythematous eruptions with some frequency, and hypertrophy of the gums often accompanies their administration. They are chemically related to phenylethylhydantoin, which was recommended in chorea, but is now seldom used, and which gave rise to an erythema on the ninth day of administration in almost every case. The hydantoin eruptions seemed to be directly related to dosage and might almost be regarded as forming part of the pharmacological action of the drug.

Mepacrine.—In addition to producing a generalized yellow discoloration of the skin this drug may cause curious and characteristic skin lesions which usually do not appear until it has been administered regularly for from three to six months. The hands, feet, neck, face, eyelids, and pressure points on the trunk are the areas commonly affected, either together or singly. To begin with, the lesions are vesicular and pseudo-eczematous in character. They may remain in this state for some time, but are usually followed or accompanied later by the appearance of slate-blue areas of discoloration which may become psoriasiform or bullous in character and which are followed by the development of hypertrophic papules or nodules resembling lichen planus. These lesions persist for months, and healing may be accompanied by scar formation and pigmentation. Dryness and follicular hyperkeratosis may be a feature of the skin not affected by an active eruption.

Biological Preparations.—With the exception of the erythema of nicotinic acid, which is constant and can be regarded as a pharmacological effect, skin eruptions do not seem to be produced by purified vitamin fractions. Generalized erythema and urticaria have been ascribed to oestrogen and insulin therapy, but must be extremely rare. A local urticarial reaction at the site of injection is, however, common with insulin. The acne of androgen therapy can be regarded as physiological.

Antihistamine Preparations.—Most curious of all drug eruptions are the few apparently fully authenticated eruptions attributable to "benadryl." These are erythematous and pruritic in nature. In view of their occurrence and the fact that, with the exception of the urticarial type of reaction, drug eruptions do not appear to be much influenced by the administration of antihistamine preparations, it would seem doubtful if histamine plays a frequent part in their development.

Fixed Eruptions

Certain drugs produce what are known as fixed eruptions. By this term is meant that the eruption always recurs on the same area—that is, it is the site which is fixed; the duration of an attack may vary within wide limits. Phenazone (antipyrin), phenacetin, arsphenamine, quinine, sulphonamides, and particularly phenolphthalein are the drugs which most often cause fixed eruptions. The usual lesion is a clearly demarcated erythematous plaque of varying size and duration which appears on any part of the body shortly after the ingestion of the drug (Fig. 5). The eruption often leaves residual pigmentation, and it recurs on the same site if the drug is again administered. There may be one or several plaques, and if repeated recurrence takes place new sites may develop lesions in addition to the old. Occasionally the lesion is urticarial or bullous. The reaction takes place only after ingestion of the drug, and testing the "fixed site" with the drug produces no response. It has been found possible to transplant the reactive skin to other areas. It is curious that the sensitivity appears to be strictly localized, and such eruptions are interesting from the point of view of the general problem of distribution in diseases of the skin.

FIG. 5.—Fixed eruption due to phenolphthalein.

Diagnosis

A perusal of detailed lists of drugs and the eruptions which have been noted to occur in association with them reveals the fact that an erythema—scarlatiniform, morbilliform, or purpuric—is common to them all, and that in only a few are additional types of lesions seen. In most cases an initial diagnosis of toxic erythema is all that is possible, and thereafter an investigation of possible "toxins," including drugs, is initiated. The history of drug ingestion leads to the suspicion of a drug eruption, and the withholding of the drug and the subsequent disappearance of the eruption strengthen it. In the case of a commonly used drug previous experience of this kind tends to confirm the suspicion to some extent. Unfortunately no form of skin test can be relied on to demonstrate cutaneous hypersensitivity to a drug administered internally, and it is only when the eruption is deliberately reproduced by the readministration of the suspected drug that the association is satisfactorily proved. While such proof is desirable it may be extremely dangerous to attempt to obtain it in view of the possibility of the development of a reaction of much greater severity than the initial one. It is not a procedure to be lightly undertaken in every case, and is to be avoided absolutely when such drugs as the heavy metals or iodides are suspected.

The history of recent ingestion of a drug may not be forthcoming in suspected cases, owing to the patient's memory being unreliable, to false denial, or to the drug

having been unwittingly ingested in the form of a food preservative, a flavouring, or a colouring agent.

Drug eruptions may simulate classified skin diseases fairly closely, but there is always some feature which is atypical. To appreciate this, considerable experience of the appearances of the classified skin diseases may be necessary. The erythema is usually florid in type and its mode of extension, duration, and regression erratic, and this taken in conjunction with extracutaneous symptoms and biological tests serves to distinguish it from the eruptions of the infectious fevers and syphilis. The administration of the heavy metals carries with it the responsibility of being on the alert for the development of skin eruptions. Bromide and iodide eruptions may be mistaken for acne vulgaris and dermatitis herpetiformis, and in their localized form for gummata or manifestations of reticulosis.

Treatment

Extensive eruptions such as those due to gold, organic arsenical preparations, and some types of sulphonamide eruption should be treated in hospital when possible. Prolonged rest in bed, careful nursing, and extensive local treatment are necessary, and the fluid intake must be well maintained. Local applications are directed towards the relief of itching and the restoration of altered skin structure to normal, and mildly astringent lotions and bland pastes or creams are suitable. In the presence of lichenoid lesions, which are usually persistent in character, crude gas tar applications and superficial *x*-ray therapy are useful.

Dimercaprol ("B.A.L.") is most useful in organic arsenical eruptions; it seems to check extension and hasten recovery, and is superior in its effect to intravenous injections of sodium hyposulphite. In gold dermatitis dimercaprol tends to relieve the intense itch but does not appear to have a marked effect on the skin changes. It is administered by intramuscular injection as a 5% solution in oil as follows: 2 ml. three times daily for the first 24 hours, and for the succeeding seven to ten days 2 ml. once or twice daily depending on the severity of the eruption. Antihistamine drugs may relieve itching, but with the exception of urticarial reactions they do not benefit the eruption greatly, and it must be remembered that eruptions have been attributed with good reason to the antihistamine preparations themselves. Severe symptoms of collapse, dehydration, and blood dyscrasias, and psychotic manifestations may accompany the eruption and call for appropriate measures.

As a rule attempts at desensitization have met with failure, but in the case of penicillin and the sulphonamides some success has been claimed from gradually increasing the dosage from an initial minute amount.

Conclusion

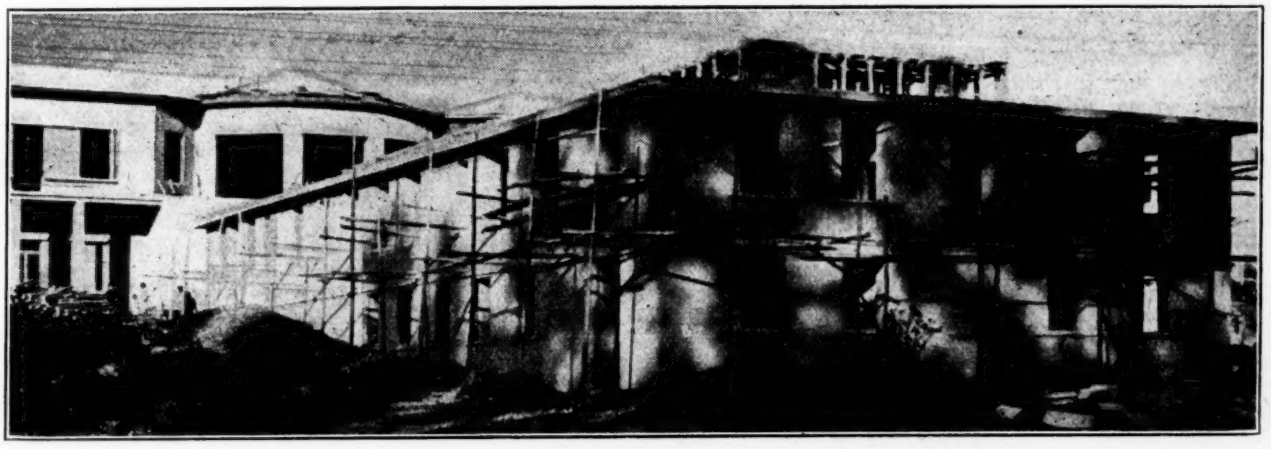
In conclusion it is safe to forecast that as new drugs are introduced it will be found in due course that the majority, if not all, will cause eruptions in some proportion of the population to which they are administered. It will continue to be a question not of whether the new drug is capable of producing an eruption but whether a skin lesion which has appeared during its administration is being caused by it, and the list of drugs recorded as having produced a rash will probably be lengthened by each addition to our stock of remedies.

PRINCESS TSAHAI MEMORIAL HOSPITAL

The Princess Tsahai Memorial Hospital is being erected in memory of the daughter of the Emperor Haile Sellassie, who trained for five years as a nurse in this country and died in Ethiopia at the age of 22 while attempting to introduce British standards of nursing into her own country. A partially constructed hospital was kindly offered to the Memorial Council by the Emperor, and the central building with accommodation for 92 patients is rapidly nearing completion. Four additional wings have been planned, and these should bring the total number of beds to 250. A two-story out-patient department has been built for medical, surgical, obstetrical, and gynaecological patients, and in addition there are special departments to deal with eye, ear, nose, and throat complaints, dentistry, venereal disease, and antenatal work. The dispensary is also located here. An annexe has been built at the back of the main building consisting, on the ground floor, of a kitchen department with electrical equipment, and, on the floor above, two operating theatres and an *x*-ray department, an anaesthetic-room, a dark-room, and other facilities necessary to such a surgical unit. There is a corridor linking this annexe to the main building, and an electric lift for both passengers and beds.

Future Training School

It is hoped in time to build a pathological laboratory and also to obtain a building in the neighbourhood to house class-rooms, a reference library, and other facilities for



The Out-patient Department of the Memorial Hospital under construction.

teaching so that the hospital can be developed as a nurses' training school for Ethiopian women. It is proposed to follow the normal three years' course carried out in this country, and after this there will be two alternative post-graduate courses: one to train nurses as midwives and instructors in antenatal care; the other to train them to take charge of clinics and dispensaries in isolated areas which are rarely visited by fully qualified doctors. In order to carry out this training it is planned to develop the obstetrical and gynaecological unit as well as the pathological laboratory, the dispensary, and the electro-therapeutic department. In addition, research work will be done in the field of tropical medicine, dietetics, and nutrition—factors of importance to Ethiopian economics. In time it is hoped that it will be possible to found a medical school which will eventually take its place in a fully developed university.

The majority of the medical staff have already been appointed, but as the hospital develops and expands it will be necessary to recruit additional trained nurses and possibly a second physician with specialized knowledge of tropical diseases. Lieutenant-Colonel W. Byam, O.B.E., who has been appointed as medical superintendent, was at one time in medical charge of the Eastern Sudan bordering on Ethiopia and Eritrea, and until lately was lecturer in tropical medicine in the medical school of St. George's Hospital. Others already appointed include Mr. H. C. Fletcher-Jones as senior surgeon, Mr. L. B. Cohen as surgeon, Dr. H. W. Stark as physician, Mrs. M. Pollett as matron, Miss V. L. G. Daish as assistant matron, Miss A. Sharpe as sister tutor, and Major G. B. Smitham as supplies officer. A gynaecologist and obstetrician, and a pathologist with specialized knowledge of tropical diseases, are still required, as are sisters and nurses with an aptitude for teaching and a willingness to take part in building up the hospital as a centre of instruction from which trained personnel will go forth to minister to the needs of the millions in Ethiopia who now lack medical care and advice.

The Memorial Hospital Council is urgently desirous of raising approximately £3,000 to pay for equipment already dispatched to the hospital. Donations will be gratefully acknowledged by the honorary treasurers, Lord Horder and Lord Amulree, c/o Messrs. Gould and Prideaux, 88, Bishopsgate, London, E.C.2.

Reports of Societies

MORTALITY SEX RATIOS

FRAILTY OF MAN

For the last 100 years in England and Wales there has been a higher general death rate among men than among women. No satisfactory explanation has been found for what some would regard as an unfortunate disadvantage, and Dr. W. J. MARTIN did not offer one when he addressed the Royal Statistical Society at a meeting on March 28, with the president, Professor A. BRADFORD HILL, in the chair. In a paper on "A Comparison of the Trends of Male and Female Mortality," Dr. Martin began by pointing out that this sex difference seemed to be of a permanent nature, and it was not peculiar to this country, or to any particular set of living conditions known to affect the general death rate. Though a satisfactory explanation had not been found for the male excess in the general rate, for some causes of death a part of the difference between the sexes could be ascribed to occupational hazards, physiological factors, or social habits.

The best-known examples of these three factors were pneumoconiosis and other occupational diseases of the lung, diseases of the thyroid and parathyroid glands, and diseases in which previous indulgence in alcohol affected the prognosis. The second group showed an excess of female, the first and third an excess of male, mortality. During the last and in the early years of the present century, when the range of employment available to women was restricted, occupational risk was thought to account for a large part of the sex difference. However, the large increase in the proportion of women engaged in industry in recent years had not, so far as could be ascertained, affected the mortality sex ratio.

An interesting feature of the excess of male over female mortality, throughout the 100 years covered by the returns of the Registrar-General, was its relatively steady increase during the century. In 1841–5 the age-adjusted male mortality was 9.6% higher than the female, while in 1931–5 it was 27.6%.

Two important factors which influenced mortality—the occupational risk and the risk due to social and environmental conditions—exerted different pressure in the two sexes. If females were more affected by home environment than males, then improvement of living conditions might be expected to lower the mortality more for females than for males. Although this hypothesis seemed a plausible explanation of the relatively greater decline in female mortality during the nineteenth century, it could not explain its continuance until now. During the present century, particularly in the past two decades, conditions of work had improved, hours of work had been curtailed, and many of the gross industrial risks had been minimized. It would be expected that any improvement in conditions of work would affect males more than females, yet the female death rate had continued to decline faster than the male; in fact the relative rate of decline had tended to increase during recent years.

Dr. Martin then discussed various causes of death in 1921–39, and showed that in every group the standardized death rate was higher for males than for females in 1921, except in cancer, where the sexes had an approximately equal death rate. For diseases of the respiratory system, tuberculosis, diseases of the digestive system, and for all causes, the rate of decline in mortality was greater for females than for males. The cancer death rate had declined slowly for females but had increased for males during the 20 years. The death rates from heart disease and violence had increased during the 20 years; that from heart diseases had increased faster among males than among females, but the rate of increase in the death rate from violence had been twice as great among females as among males.

The death rate varied in the different regions of the country. Other factors associated with mortality (e.g., housing, occupational and social class distributions) also differed. The increase in the ratio of male to female mortality within the regions did not form such a regular progression as was found for the ratio in the country as a whole. The level and rate of increase varied between the regions. The ratio was higher throughout the period in London than elsewhere. The difference between the highest and lowest ratio of a region was greatest in the south-eastern region, while in the northern region and Wales the ratio showed the least change. He gave figures to support the theory that the level of the ratio within the regions was influenced by the movement of the female population.

Specific Age Comparisons

By means of some penetrating arithmetical analysis Dr. Martin then discussed how the mortality sex ratios have changed in the course of years in various age groups. He showed, for example, that at ages 0–1 the ratio of male to female infant mortality had been at a constant level during the first 60 years of the last 100; it had then risen during the first five quinquennia of this century and remained almost stationary. The rise in the mortality ratio had started at the same time as the fall in infant mortality. The increase in the ratio, although small, was interesting. On the average, baby boys had the same environment as baby girls. Modifications in the classification of causes of death, made to meet the increase in medical knowledge, made it impossible to trace the course of individual diseases throughout the century, but the rise in

the mortality ratio appeared to occur for most causes of death. The size of the mortality sex ratio seemed to be some function of the size of the infant mortality.

Mortality from accidents and negligence at ages under 1, which fell rapidly during the first 40 years of the present century, had risen appreciably during recent years.

Apparently boys did not have the care and attention that their sisters had or they succumbed to injuries more easily. A difference in the male and female character—for example, a greater desire for adventure or exploration—in the boys could hardly be an explanation of the whole of the male excess, since, at any rate in the first year of life, the child contributed little to the train of events leading to the fatality.

In adult life the mortality sex ratio had increased for each age group throughout the century. It had increased with increasing age from 25–29 to 55–64, and then declined; for the oldest group, 85+, the ratio had shown the smallest change of any group. In each age group most causes of death had now a higher mortality ratio than the ratio from all causes at any time during the century. Exceptions were rheumatism and diseases of nutrition, which had a very low ratio in each age group, cancer up to age 54, and diseases of the nervous system from age 45. There had been a general rather than a specific increase in the mortality sex ratio during the period.

Social Class

An examination of the mortality sex ratio showed that the well-known upward gradient of mortality with social class had a varying slope for males and females. The values of the mortality sex ratios for 1930–2 were:

Social Class	Ages				
	25–34	35–44	45–54	55–64	65–74
I	130	132	158	163	166
II	112	131	149	154	148
III	110	128	141	140	145
IV	114	139	146	139	141
V	101	132	153	139	147

The size of the mortality sex ratio, for different individual causes of death, varied considerably. While it was difficult to assess the relative importance of specific causes which contributed to the high ratios of classes I and II, that of heart disease was very large. The mortality sex ratios for tuberculosis and pneumonia were also very large.

Fewer "Other Causes"

In the subsequent discussion Mr. L. G. K. STARKE emphasized that this country could be proud of its vital statistics. He noticed that deaths from "other causes" were decreasing in number. Why the female of the species was hardier than the male was a difficult problem, but hardly one for the statistician. Deaths from violence, especially road accidents, showed particularly how sex ratios of mortality varied with age. The male excess in infancy was puzzling, for then the environment of the sexes was the same. Dr. J. O. IRWIN made an ingenious analysis of Dr. Martin's paper, and pleaded for the use of regression analysis to treat problems such as those raised here.

Dr. W. P. D. LOGAN defended the Registrar-General's mortality statistics from the pessimistic aspersions cast by Dr. Martin on their comparability over certain years. He thought the sex difference of deaths from violence in infancy was largely due to deaths from suffocation. He had serious doubts whether these infants did die from suffocation. The cause in many cases was probably fulminating pneumonia, a disease to which males were more liable to succumb. The high male excess in deaths from drowning among children was due to the greater adventurousness of boys. Many had been drowned in A.R.P. tanks during the war. Dr. D. SWINSCOW suggested that mortality sex ratios for narrowly defined diseases were remarkably constant throughout the years and specific to the disease. He thought that they might be used to test the homogeneity of records of deaths.

Mr. R. D. CLARKE thought that coronary thrombosis contributed largely to the excess of male mortality in social class I.

Professor BRADFORD HILL recalled that the stillbirth rate was higher among male than female calves. But, as he said, the mortality rate later depended on the destiny of the animal—meat or milk.

MURDER

As Dr. KEITH SIMPSON prophesied, his lecture on "Murder" to the Medical Women's Federation on March 21 brought his audience down to earth—or even below it. Punctuated by some earthy slides, his talk ranged from inside information on infanticide to the harrowing horrors of homicide. He began by defining what he meant by "murder" and indicating in what ways it differed from manslaughter and justifiable homicide. When dealing with an adult who has died a violent death the first question to be decided is, "Is this murder—or suicide?" This is not so in the case of infants, however. If a newly born child is found with a ligature round its neck there can be only one interpretation. In this connexion Dr. Keith Simpson vouchsafed the interesting fact that a woman who is bent on doing away with her newborn babe never seems to use the umbilical cord for the purpose—in spite of the fact that it is fairly handy at the time and that it is frequently the cause of accidental death anyway.

A great deal of valuable information can be inferred from the position of a body, and Dr. Simpson reminded his audience of their responsibilities as trained observers. He told of the doctor who was called to see a patient, supposedly recovering from influenza, who had suddenly died. The doctor finished his round of calls before reporting the matter to the coroner, because he failed to observe the marks of strangulation on the patient's throat. It was some seven hours later that a second body was found, and many more before the assailant was tracked down—a long way from the scene of the crimes. Details, Dr. Simpson said, were often of the utmost importance in deciding between homicide and suicide: although you can tie the knot at the back of your neck when strangling yourself you are much more likely to do it at the front. He described the way in which medical training helped in hunting down assailants and identifying victims. A few molars left in a charred skull were recognized and identified by a dental surgeon; on another occasion the tooth-marks found on a victim's body were directly responsible for identifying the assailant. An apparently innocent pebble seen with many others in the sludge of a backyard became—when observed with the eyes of a doctor—a large gallstone; the sludge was then examined more closely and further traces of a missing woman were found. There were occasions, however, when Dr. Simpson had been set impossible tasks—as, for instance, when he had been presented with the mummified remains of an infant and asked to find out by what means it had been killed. This particular specimen had been discovered by an eager dustman looking through the day's takings to see what he could find. The master of the house had relegated a cardboard box containing the remains to the refuse bin, but not until it had spent some time in the attic. Some time before this his Irish servant girl had given notice, and he observed this cardboard box sitting on a radiator after she had left. Apparently he was not overpowered by curiosity, for he did not open the box, but when after a few days he felt it was getting a little high he sprayed it with some disinfectant. A little later he put it in the attic and thence into the dustbin.

Dr. Simpson is an accomplished raconteur, and some of his experiences stretch an average imagination to the uttermost. For instance, there was the girl who was charged with murdering her baby, which was found in a brown-paper bag at the bottom of her bed. She denied all knowledge of it, saying that somebody must have dropped it there when they were passing. When the policeman interviewing her expressed a little surprise at this new method of having babies the girl said that nothing like this had ever

happened to her before, so she would not know. Perhaps the most grotesque tale, however, concerned the two friends who, having imbibed a great deal of intoxicating drink, then retired to the apartment of one of them to continue their revels. The guest finally staggered into the bed belonging to the owner and fell into a drunken sleep. The owner of the apartment continued drinking until he too climbed into his bed in a drunken stupor. He was very surprised to find when he got there a dummy, or what he took to be a dummy. (But then, his friends often played that sort of practical joke on him.) Incensed at this he picked up a knife and stabbed the "dummy" viciously in many places and threw it out on to the landing. It bled a little; but then, when his friends played a joke on him they did it properly. Such was his defence when he was charged with the murder of his mate. The "dummy" was found at necropsy to have a blood-alcohol of some 450 mg. per 100 ml., indicating that he must have been very drunk indeed. The jury found the accused man not guilty.

It is clear from Dr. Simpson's lecture that advances in medical science are available to potential murderers as well as to the forces of law and order, but the balance is probably in favour of the latter.

THE HISTORY OF NUTRITION

OSLER CLUB MEETING

In a survey which ranged from the earliest prehistoric times to the nineteenth century Dr. H. M. SINCLAIR, speaking to the Osler Club on March 30, selected certain landmarks in the history of nutrition for more detailed consideration. The Greeks were the first to give serious attention to dietetics. Developing a body of knowledge which had been accumulated by the gymnasts, the men in charge of athletic training, Pythagoras insisted that dietetics should be the first line of treatment in all diseases. From the emphasis which it places on this view the Hippocratic oath, some of the aphorisms, and at least four of the Hippocratic treatises are obviously not Coan but Pythagorean in origin. Working in Alexandria in the third century B.C. Erasistratus carried out experimental work on the nature of weight-loss during fasting, investigations which were neglected until Sanctorius resumed them nearly 2,000 years later. Although Galen stressed the importance of dietetics in infancy the Romans added little to previous knowledge, and it was not until the sixteenth century that any advance could be recorded. Leonardo seemed to have an idea of the nature of oxidation and of innate heat. Paracelsus regarded disease as dysfunction and was the first to suggest a chemical aetiology for gout and stone.

Contrary to Still's opinion, Dr. Sinclair thought rickets was a new disease which, for some unknown reasons, suddenly arose in England about 25 years before Daniel Whistler's first description of it in 1645. Among the few contemporary literary references to the disease there is one by Sir Thomas Browne in which he states that in Norfolk the livers of birds, especially of rooks, were found to produce a cure. In the middle of the following century one of the finest controlled experiments in the early history of nutrition was carried out by the naval surgeon James Lind in an attempt to find the most effective antiscorbutic. The belated result of this test was the institution by Blane in 1795 of the compulsory lime-juice issue to men of the Royal Navy. In the nineteenth century, with the rise of the French and German schools and the work of Gay-Lussac, Bernard, and Liebig in metabolic chemistry, the foundations of the modern science of nutrition were laid.

In the subsequent discussion Professor V. H. MOTTRAM carried the story to our own time with his personal recollections of Karl von Voit, Graham Lusk, and Sir Frederick Gowland Hopkins. He characterized Hopkins as "a dominating intellect and a deprecating soul" and described his reception of the news that he had been awarded a Nobel prize as a good example of his humility, for, "What shall I do," Hopkins asked him, "when I am found out?" Dame HARRIETTE CHICK supplemented the story of scurvy with an account of the discovery, during World War I, that the lime-juice issue was no longer effective as an antiscorbutic because the source of supply had been changed from the Mediterranean to the West Indies round about 1850. Investigation showed that the West Indies sour lime was far inferior to the Mediterranean product and contained only about 25% of the amount of vitamin C contained in fresh lemons.

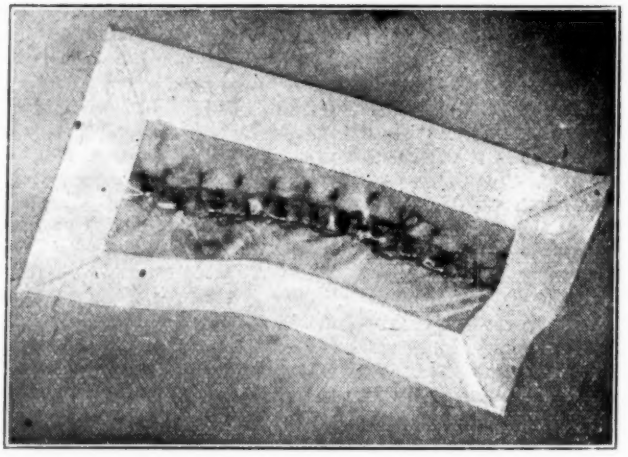
Mr. A. L. BACHARACH commented on the belief that birds' livers could cure rickets and gave reasons for doubting that any animal liver contains vitamin D_3. Professor R. A. PLIMMER paid a tribute to the great work done by Dr. Chick, especially in pellagra. Dr. GEORGE GRAHAM, referring to fashionable preoccupations with obesity, gave some specimen menus from Banting's *Essay on Corpulency* and complained that those who were responsible for producing diet sheets made too little use of the work of modern investigators in order to make them varied and attractive.

Preparations and Appliances

A POST-OPERATIVE WINDOW DRESSING

Mr. A. DAVIS BEATTIE, F.R.C.S., Mr. HAROLD DODD, CH.M., F.R.C.S., and Professor W. C. W. NIXON, F.R.C.S., F.R.C.O.G., write: The regular inspection of all operation incisions may be of great advantage in the early recognition of wound sepsis and in the detection of incipient wound disruption. But the danger of this procedure lies in the possibility of inaugurating infection of the wound through secondary contamination.

In order to allow of such examination without the attendant risks the transparent plastic dressing illustrated has



been developed. It permits of critical examination of the lesion at any stage of the healing process. It can either be used as a single strip dressing with open ends or completely sealed by additional plaster strips so as to create a closed dressing. But, even if the ends are left uncovered, secondary contamination of the wound does not seem to occur. This window dressing has been in use by us for over six months on all types of operation incisions, and during this period nearly 300 cases have been treated without any untoward results.

The dressing is applied in the theatre at the conclusion of the operation and is left in position until sutures or clips need to be removed. It is then renewed for any further necessary period until healing is complete. No instance of sensitivity to the adhesive has yet been observed. The type of plastic used along the borders is readily shaped to any lateral curvature of the incision, and moulds easily to the body contours. The central transparent plastic material does not adhere to the wound or the suture material employed; it gives an excellent view of the incision line and is strong

enough to resist all normal post-operative stresses. It is also waterproof, thus permitting more complete bed-bathing of the patient than is possible with normal dressings; and its lesser bulk is of considerable advantage where early ambulation is permissible.

The dressing has the added advantage that, owing to the impregnated antiseptic in the gauze covering, it remains sterile after three weeks' exposure to air. It is thus safe to use from the original packets during this period, and its residual antibacterial properties help to inhibit the growth of organisms in the wound area. A factor which makes the availability of this window dressing singularly timely is the present shortage and threatened famine of gauze and cotton-wool. Moreover, it is actually cheaper to use than the ordinary post-operative dressings of these materials.

We are much indebted to Messrs. Dalmas, of Leicester, for their courtesy and help in the evolution of this dressing.

Correspondence

New Operation for Peptic Ulcer

SIR,—Mr. Stanley Aylett (March 3, p. 454) is to be congratulated on his ingenuity in devising a new operation for the treatment of peptic ulcer. His article recalls to mind the experiments on dogs reported by McCann in 1929. That worker, in an extension of the Mann–Williamson investigations, performed the identical operation which Mr. Aylett now recommends for the treatment of peptic ulcer in human sufferers. Of McCann's 26 dogs 80% had developed ulcers within three months of operation. The ulcers were situated just beyond the gastro-jejunal suture line. In common with Mr. Aylett, McCann investigated the post-operative gastric acidity; it is noteworthy that they both got the same result—normal levels of acidity. Their interpretations of this finding differ; whereas Mr. Aylett regards it as an indication of the effectiveness of the duodenal juices in reducing gastric acidity—though he leaves it to be implied that the pre-operative levels were abnormally high, a by no means invariable finding—McCann interpreted it to mean that the method was ineffective in reducing gastric acidity, and says, "Whether the duodenal secretions beyond the pylorus are partially or wholly removed, or whether they are shunted from the duodenal to the gastric side of the pylorus, the concentration of the acid of the chyme that passes the pylorus remains constant. Consequently all these ulcers have occurred with the passage of chyme of normal acidity by the pylorus into a segment of intestine where their action is not terminated by the duodenal alkalis normally present on the distal side of the pylorus." It must be stated, however, that McCann reported post-operative fractional test-meals on only three dogs; also, that Mr. Aylett found complete post-operative achlorhydria in some of his patients.

Mr. Aylett doubtless considered McCann's work and felt justified in proceeding despite it. I feel, however, that as he gave no references the attention of others who may be considering the use of the operation which he describes should be called to these experiments. Oliver (1949) has recently referred to McCann's work.—I am, etc.,

Stockholm. GORDON FERGUSON.

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SIR,—The principle of total return of duodenal contents to the stomach, which forms the basis of the operation for peptic ulcer described by Mr. Stanley Aylett (March 3, p. 454), was suggested by Paterson, of London, in 1909, and later applied by Schmilinsky and by Kummel. Schmilinsky (1918) reported eight of his operations, with a follow-up of three patients, one of whom had died of perforated jejunal ulcer. An operation similar in principle was among those tried out in Wangensteen's laboratory for its protective value in dogs stimulated to excessive secretion of acid by histamine implantations. Unlike gastrectomy the operation failed to prevent the development of jejunal ulcers (Wangensteen, 1950).

Finney's pyloroplasty also allows direct entry of all bile and pancreatic juice direct into the stomach, but has not been found dependable in the prevention of recurrence of ulceration in intense hypersecreters of acid. Nor has a low Polya gastrectomy, in spite of the total entry of duodenal juices into the stomach which results when no baffle is constructed.

Perhaps the neutralization of gastric contents by duodenal juices is less adequate in these people than Mr. Aylett hopes, and this would be suggested by the work of Berk *et al.* (1942). One of Paterson's patients had a jejunal fistula well distal to a gastroenterostomy stoma, where complete mixing might have been expected, yet it discharged fluid containing 0.072% free HCl (20 milli-equivalents per litre).

Mr. Aylett's later reports on follow-ups will be awaited with interest. If jejunal ulcers occur the treatment of them may, it seems to me, present a problem very difficult of solution.—I am, etc.,

London, W.1. H. DAINTREE JOHNSON.

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SIR,—This operation, described by Stanley O. Aylett (March 3, p. 454), would appear to be identical with the McCann modification of the Schmilinsky procedure which was introduced in 1918 in an attempt to neutralize the gastric acidity by total intragastric regurgitation of the duodenal secretions. That it fails to do this adequately has been shown by the high incidence of gastro-jejunal ulceration which has followed this type of operation both in experimental animals and in human patients.

In 1929 McCann reported the development of ulcers at the new gastric outlet in 80% of a series of 26 dogs when the total duodenal secretions had been drained back into the gastric fundus. The experiment was repeated in 1937 by Maier and Grossman and two dogs out of a total of twelve developed gastro-jejunal ulcers.

Wangensteen and Lannin showed that neither the Schmilinsky operation, where the duodenal loop is anastomosed to the gastric antrum, nor the McCann modification, where the loop is anastomosed to the fundus, would protect dogs from developing peptic ulceration under the prolonged effects of histamine stimulation.

In 1940 Wangensteen reported three cases where this type of procedure had been performed on human patients. One of the patients died from perforation of a gastro-jejunal ulcer four months after the operation. Another died 52 days after the operation from uncontrollable gastric haemorrhage. These experiences led him to classify it as a "highly undesirable type of operation."

Wangensteen explains the failure of this type of operation on the grounds that total intragastric regurgitation of the duodenal contents causes interminable prolongation of the gastric phase of gastric secretion and probably intensifies the intestinal phase as well, with the result that the acid-secreting cells in the residual gastric pouch are kept in a state of constant stimulation.

In the light of these observations, the revival of the McCann operation must be regarded with caution. It is to be hoped that the patients who have been submitted to this operation will be studied carefully and that their subsequent progress will be reported in full before the operation comes into common use. It will be readily appreciated that, should gastro-jejunal ulceration follow this operation, the task of disconnecting the anastomoses and performing an orthodox gastric resection might present considerable technical difficulty and not a little risk to the patient.—I am, etc.,

Ottawa. COLIN D. L. CROMAR.

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Gastrectomy

SIR,—Having read the article by Professor C. Wells and Mr. R. Welbourn (March 17, p. 546) it appeared to me that, while the accepted operations of gastrectomy are curative for a disabling and occasionally lethal lesion, they are bringing in their train a new set of syndromes and even new operations to cure them, not a desirable state in this enlightened day, and I was disappointed to see that relatively little emphasis was placed on prevention of these undesirable after-effects, most of which can be referred to the abnormal new mechanics introduced into the gastro-intestinal tract.

In my own opinion the Billroth I operation is, as was stated in the article, much less liable to have unpleasant sequelae and should, I consider, be performed in every case requiring gastrectomy, unless there is an adherent duodenal ulcer.

There is one fallacy in connexion with this operation which has gained common acceptance, and that is that it is not possible to do a true radical gastrectomy. This is not so. The more stomach removed, the easier to bring round the stump, as the vasa brevia must be divided, and, this having been done, the fundal stump is entirely mobile, hinging merely on the cardiac end of the stomach.

The anastomosis is technically a little more difficult than in any modification of the Polya–Sherren operation, but the immediate post-operative course is always pleasanter, and even if the small stomach "dumps," it dumps into the normal receptable for chyme. Also we have eliminated any chance of kinking or compression of a jejunal loop.

Professor Wells and Mr. Welbourn mention the chance of recurrent ulceration, but I have never seen this and I see no reason why if the amount of stomach removed is adequate, as it should be, it should occur any more commonly than after any other type of gastrectomy.—I am, etc.,

Swansea. B. BRENDAN HICKEY.

Conservative Treatment of Perforation

SIR,—When Hermon Taylor demonstrated so clearly that non-operative treatment could be successful in cases of gastro-duodenal perforation he did much to solve the problem of how best to treat the occasional patient whose local or general condition made a laparotomy undesirable. Many of us have now employed this method for some years on carefully selected patients with satisfactory results. During the last year or two, however, a few enthusiasts have advocated a much wider adoption of this conservative plan as an alternative to surgery in cases where no clear contraindications to laparotomy are apparent, a recent article (March 31, p. 675) claiming ". . . that immediate operation in simple gastro-duodenal perforation is no longer necessary, and that any operative intervention should be reserved for such complications as may arise." Many will feel that this statement should not pass unchallenged.

Until comparatively recently the mortality of surgical intervention was around 15% and there was every reason to be dissatisfied with this figure and to seek an alternative method of treatment, but during the last few years the mortality rate in cases treated by simple closure of a perforation has dropped to a very low figure indeed, and the few patients who die usually do so either on account of factors unconnected with the method of treatment adopted or because the local condition has been unusually complicated from the start, for instance by several previous operations on the stomach.

Patients without grave constitutional disease do not now die after surgical closure of an uncomplicated perforation, and, although it is true that some perforations are small and found at operation already sealed off, I personally have not been struck by the frequency of this finding and I do not know of any means of determining the size of a perforation before operation with any degree of accuracy.

Mr. E. Scott is to be congratulated on the skill and conscientious attention to detail which he and his nursing staff have used to such good effect on the series of cases he reports. If he continues thus until a significant number of cases have been treated, the likely result is that his figures will be better than those for surgical closure in the cases exhibiting a clear contraindication to laparotomy, but that he will risk losing unnecessarily one or two of his "good risk" cases. His overall figures will probably be not greatly inferior to those obtained by surgery. Where he goes wrong is in not realizing that the best results of all are to be obtained by a careful selection of cases, treating with the conservative plan those cases in which a clear indication against laparotomy exists, and operating upon the others.

The greatest danger in his article, however, lies in the fact that, if his advice is taken literally by all and sundry, some will fail to realize that the successful application of non-operative treatment requires not less but more skill, clinical observation, and attention to detail than operative treatment. Unless this is realized and the conservative plan applied as successfully as in Mr. Scott's cases, to refuse surgery to otherwise healthy adults with uncomplicated perforations can lead to nothing but disaster.—I am, etc.,

London, W.1. RODNEY SMITH.

SIR,—I was interested to read (March 31, p. 675) about Mr. Edmond Scott's experiences in treating acute perforations conservatively without operation. There is one point, however, which he does not mention, and that is the usefulness of operation as a diagnostic measure. No doubt in the series of cases he quotes there was a reasonable chance of their being all non-malignant gastric or duodenal perforations, but my own feeling is that the non-operative treatment of perforations in the hands of any but the most expert diagnosticians may subject the patient to further hazards.

As a one-time surgical registrar I needless to say lived in fear and trepidation of discovering that my perforations when opened would not be perforations, and it was always with considerable relief that one found an obvious perforation surrounded by fibrinous exudate, but one sometimes felt that this good fortune was in the lap of the gods, and there can be few surgically minded persons who cannot remember the malignant perforation, the perforated appendix, and other abdominal catastrophes simulating in every detail the true peptic perforation. I am sure that there are few experienced surgeons who would not admit the possibility of a misdiagnosis in a strongly suspected perforation.

I think the matter can be summed up simply by saying, "Yes, by all means consider treating a perforation conservatively, provided it is absolutely certain beyond any possible doubt that it is a non-malignant simple perforation of the stomach or duodenum."—I am, etc.,

Wembley, Middlesex. M. E. ARNOLD.

Chloroquine

SIR,—Results obtained with chloroquine diphosphate ("aralen") used as a suppressive and also for the treatment of a small number of cases of *P. falciparum* malaria in a very malarious district of the Gold Coast may be of interest.

Ten Europeans, who had previously been taking either quinine, mepacrine, or proguanil as a suppressive, changed to chloroquine and started with a loading dose of four tablets (1 g.) during the first week, after which they carried on with two tablets (0.5 g.) weekly as recommended by the makers. Within three weeks three of them were suffering from clinical attacks of malaria with parasitaemia. Thereupon all but two changed back to their original suppressive. The two continuing to take chloroquine have so far been free from attacks.

The three cases that occurred were treated with chloroquine. Two received the recommended course of 1 g. as an initial dose, followed by 0.5 g. eight hours later, and

0.5 g. on each of two successive days, making a total of 2.5 g. The third received 5.5 g. over a period of nine days. All had symptoms and parasites in their blood on the completion of treatment, although one of those on the smaller dose cleared on the fourth day. The other two were started on mepacrine after one day's observation and rapidly improved. An indication that the drug was being absorbed in the case that received 5.5 g. was given by the fact that pronounced visual disturbances were produced. This, and nausea in the case of the one woman taking it as a suppressive, were the only toxic symptoms recorded.

Although the number of cases is so few, the response cannot be considered altogether satisfactory. The reason for this may be that the parasites in this area may be resistant to chloroquine, as they are to proguanil, or that the dosage used was inadequate.—I am, etc.,

Accra, Gold Coast Colony. J. J. MESSENT.

Enlarged Prostate

SIR,—Mr. E. W. Riches observes (March 24, p. 633), "To put a patient on to self-catheterization halves his expectation of life." Perhaps the following is an exception which proves the general rule. I am looking after a patient in his 97th year who has catheterized himself regularly for 15 years with a gum elastic catheter which he keeps in a simple tin box. He has had no trouble at all, and is yet active and in possession of all his faculties. A recent specimen of urine was clear and free of albumin. Catheterization has handicapped him hardly at all.—I am, etc.,

D. I. EVANS.

Toxic Chemicals in Agriculture

SIR,—I have read your leading article (March 24, p. 628) and also the "confidential" information issued by the B.M.A. I am probably a fairly typical rural practitioner, in whose district the spraying of market garden and farm crops is general.

My reaction to this information is a desire to find a way of disclaiming in advance any responsibility for the survival of patients of mine who may be affected by these chemicals.

In my opinion it is, first, too much to expect that the workers concerned will observe the strict safety precautions considered necessary.

Secondly, the early toxic symptoms could apparently so easily be mistaken for those due to other causes, such as neurosis, heat stroke, etc., that the responsibility of early diagnosis is too much to ask of the general practitioner, this being more especially so if he is to treat every possible case either by immediate transfer to hospital or by hourly injection of atropine in 1/60 to 1/30 gr. (1–2 mg.) dose.

My final reaction is the opinion that the use of these insecticides should be prohibited until a compound harmless to man has been found.

I am no crank, I hope, but I am slightly dubious about chemical fertilizers. I have always disliked the practice of agenizing flour. I fear these chemists. I feel that this attitude may be widespread enough to warrant recording.—I am, etc.,

Bergh Apton, Norwich. W. C. WARDLE.

SIR,—In your leading article on this subject (March 24, p. 628), the statement is made that "D.N.O.C. is only cumulative when doses follow one another in rapid succession in periods of hours and not days." Experiments on human volunteers do not support this view. Daily doses of 75 mg. D.N.O.C. by mouth cause a steady rise in the concentration of D.N.O.C. in the blood. After three or four days the maximum level is attained. A further dose of 75 mg. at this stage causes a marked increase in the concentration of D.N.O.C. in the blood and this increase may be accompanied by symptoms.

Excretion of D.N.O.C. takes place remarkably slowly in man. D.N.O.C., 75 mg., was administered daily for five days. Six weeks after the final dose four volunteers still had D.N.O.C. present in the blood in concentrations of from 1 to 1.5 μg. per gramme of blood. Details of the experimental work in animals and human beings will be published shortly. We believe that absorption of D.N.O.C. in small amounts each day will result in a cumulative effect. Persons who show any symptoms and signs of D.N.O.C. poisoning should be removed from risk of further absorption for a period of at least six weeks.—We are, etc.,

D. GRAHAM HARVEY.
London, E.1. P. LESLEY BIDSTRUP.

Accelerated Development of Children

SIR,—It is a well-known fact that children to-day are bigger than the children of 40 years ago. They weigh more and are taller. Every well-meaning person is pleased: "That is the result of our child-welfare services," and they all pat themselves on the back.

But the other day in the *British Medical Journal* a writer pointed out (February 24, p. 403) that the average height and weight of the adults of this generation have not altered. This is a very important observation. It means, in fact, that although the children are bigger the adults are not any bigger. A glance at any gathering, such as a football crowd or a crowd on the pavements of our cities, seems to confirm this. What does it mean? It means that the young of our species in England mature quicker than their forebears. A child of 12 is physically three years in advance of his grandfather. In other words, although to us they appear to be children, already they are men and women, say, at 15 or 16 years of age. There are several consequences of prime importance.

Juvenile Delinquency.—One blames the education system, lack of parental control, and similar causes, whereas the most salient fact is the early maturity of the individual: man's instincts and a child's brain. Our legislation has not yet caught up with that concept. Yet it is plain that early maturity is a great factor in juvenile delinquency.

Lack of Fertility.—A great number of young people marry at early ages, which is very sound biologically, but socially is a nuisance. If marriage is delayed, say, to 25 years of age, the woman has already had about 13 years of sterile sexual maturity, which biologically is bad. No breeder of animals would wait such a long span of the animal's life before mating her. The later marriage rate of the man does not matter quite so much, but fertility does drop a little.

We must also remember the earlier onset of menopausal symptoms, the greater number of cases of impotence, and the rise in the rate of congenital malformations.

I trust that these observations may lead to some discussion; for if, indeed, the views expressed herewith are correct some readjustment is needed both in the nation's laws and in the assessment of the implications of this accelerated maturation of the human adult.—I am, etc.,

Southampton. E. SAKOSCHANSKY.

Absorption of Iron

SIR,—I read with interest your leading article on the absorption of iron (February 3, p. 231), because abnormal deposition of the element is frequently observed in the South African Bantu living on the Witwatersrand (investigations up to the present have been limited to these people).[1,2]

Haemosiderosis—apart from being a feature of haemochromatosis—can arise from a high oral intake of iron, from its intravenous administration, from diseases marked by haemolysis, and possibly from malnutrition. Since it has been found that the iron intake of these Bantu is frequently as much as 200 mg. per day, derived mainly from their iron cooking vessels,[3] the role of this high intake, as a causative factor in the haemosiderosis observed, seems worth considering. An interesting observation, barely mentioned in current reviews on iron metabolism, is that, when iron preparations are taken orally in doses of the order used in iron therapy, an abnormal amount, sometimes reaching several grammes, is absorbed by the body. Such iron is retained and not

excreted. This abnormal absorption has been observed to occur not only in anaemic persons[4 5] but also in normal or non-anaemic subjects.[5 6] It seems, therefore, that the usual response to a high intake of iron is an excessive retention; in other words, under such conditions of intake the "mucosal block"[7] ceases to operate effectively.

Returning to the local Bantu—the iron provided by their cereals, legumes, etc., is already relatively high—say, up to 40 mg. per day. When these foods are cooked in iron vessels—the ubiquitous kaffir pots and paraffin cans, also the larger iron containers used in communal feeding—this intake may be doubled. When, however, fermented maize porridge (*marewa*) and kaffir beer, of *p*H values about 3.5, are prepared, the uptake of iron may reach ten times the amount contained in the parent cereals. It must be emphasized that such food preparations are national and traditional to these people, and are frequently consumed in large amounts by men, women, and even children. Analysis of the total diets consumed and also of stools from widely different sources gives the impression that a high intake of iron, sometimes exceeding 200 mg. per day, is of common occurrence. Balance observations[4 6] have shown that an intake of this order lies within the range wherein excessive retentions are likely to occur. Can these intermittent though cumulative retentions be responsible for the haemosiderosis?

Of the other possible causes, malaria is the only common disease marked by haemolysis which, if chronic, could give rise to intense haemosiderosis. But Gillman and co-workers have pointed out that, since typical malarial livers were found so seldom in the haemosiderotic cadavers studied by them, malaria cannot be responsible for the frequently observed haemosiderosis.[2] As a causative factor, blood transfusions obviously can be neglected.

As to malnutrition, American workers have shown, with animals, that an abnormal absorption of iron may be caused by certain types of inadequate diet—for example (*a*) when composed of 80% maize or rice and 20% lard,[9] or (*b*) when deficient in pyridoxin.[10] Such haemosiderosis is increased by the presence of a high iron intake. Turning to man, one might remark that malnutrition is not new, nor is it confined to backward pigmented peoples; moreover, the phenomenon of haemosiderosis was well known towards the end of the last century. In Europe at that period poverty was not uncommon. If, therefore, malnutrition *per se* is a causative factor it is difficult to understand why able German pathologists like Quincke, who were keenly interested in the subject, failed to report a type of haemosiderosis peculiar to poorly nourished people. It could be argued that the undernourishment then occurring was too mild to provoke the phenomenon, or that the latter was of too infrequent occurrence to attract special attention. Yet our Bantu are not the most malnourished of peoples.

Surely if malnutrition is causative, haemosiderosis should be proportionately common among less-favoured inhabitants of the East. So far as I can determine there is no evidence that this is the case. Absence of reports does not, of course, establish that intense haemosiderosis does not occur, but their lack gives the impression that malnutrition *per se* is not the critical factor. On the other hand, it is conceivable that a particular type of malnutrition is involved. The point you noted, Sir, in relation to a low phosphate diet promoting the absorption of iron does not seem to have a bearing on the haemosiderosis in the Bantu, for the nature of their diet is such that their intake of phosphorus is unusually high.

There would seem to be at least three possible hypotheses on the causation of this "dietary haemochromatosis" maintained by Gillman and co-workers to be one of the manifestations of chronic malnutrition.[3]

(1) Under certain conditions the consumption of an inadequate diet gives rise to a malnutritional picture which includes, *inter alia*, kwashiorkor, pellagra, hepatic cirrhosis, primary carcinoma of the liver, and also haemosiderosis.

(2) Under certain conditions the consumption of an inadequate diet causes a lesion which, as in (1), allows abnormal absorption of iron to occur; but the amount absorbed reaches significant proportions—i.e., the haemosiderosis becomes prominent—only in the presence of a high intake of iron, the latter being common and apparently peculiar to the Bantu.

(3) The haemosiderosis is caused primarily by the high iron intake (there is no necessity to postulate a lesion of the digestive tract), in which case the diseases occurring simultaneously are fortuitous superimpositions.

A certain amount of evidence from both animals and man may be cited in support of each hypothesis, but present knowledge is insufficient to establish the probable explanation. It is necessary to know more of the character of the haemosiderosis—i.e., of its extent, distribution, and histological picture in the organs and tissues affected—and of how the incidence is influenced by malnutrition generally, by the type of cereal consumed (maize, kaffir corn, etc.), by the amount of acid-fermented foodstuffs consumed, and so forth. It is, alas, all too easy to theorize. One would be grateful for any comments your readers may care to make on this phenomenon which occurs so frequently among these people.

This letter is published with the permission of the South African Council for Scientific and Industrial Research.

—I am, etc.,

Pretoria. ALEXANDER R. P. WALKER,
Senior Research Officer, Nutrition Unit, National Chemical Research Laboratory, South African Council for Scientific and Industrial Research.

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Lung Abscess after Shock Therapy

SIR,—In reference to your annotation (December 16, p. 1377), and subsequent correspondence, may I quote my experience? In the course of 1950 five of my patients from a total of 210 treated with electro-convulsive therapy died of lung abscess. This is of course nearly two and a half times the 1% quoted in the annotation. It is noticeable that the negro, particularly the psychotic negro, seldom swallows but harbours his saliva in his mouth. I consider that this habit, combined with, in some cases, oral sepsis, may facilitate the inspiration of infected saliva during treatment and thus set up abscess formation in the lung. None of the five had been tube-fed.

Incidentally, I find that an induced fit is a satisfactory substitute for a spontaneous epileptic convulsion, but it is a puzzle to me that an epileptic requires a higher dosage to induce a fit than the non-epileptic. What of the "low epileptic threshold"?—I am, etc.,

Kampala, Uganda. G. CAMPBELL YOUNG.

Operating Theatre Technicians

SIR,—I strongly oppose the introduction of operating theatre technicians except at small outlying hospitals which cannot attract sufficient suitable nursing personnel. In these hospitals the operating theatre technician may act as a theatre porter, help to set out operating trolleys, attend to the anaesthetist, assist the surgeon in the absence of a house-surgeon or general practitioner, care for and make minor adjustments to the instruments, and help to prepare and sterilize the hospital laundry, etc., etc. In this way he saves his hospital much expense, and undoubtedly he is a very useful and permanent member of the staff.

He has no place whatsoever in other hospitals or teaching hospitals, and his presence would be an absolute waste of money unless he is going to replace some member or members of the theatre staff. What function can these gentlemen perform that cannot be carried out by an efficient

theatre sister and her staff? Surgical instruments can be maintained in perfect order by the theatre nursing staff, and major instrument repairs will of necessity require return of the instrument to the manufacturers.

How many assistants are we going to have "scrubbed up" at operation? What will become of our house-surgeons and young trainee specialists? What will the position of the theatre sister become? A theatre sister worth her salt will not tolerate this intrusion on her rights. Have surgeons, and particularly anaesthetists, become so busy that they cannot devote some of their time to demonstrating their methods to untrained theatre nursing staff? Nowadays it would appear we have no wish to help ourselves, for the anaesthetist does not want to charge his own syringes (February 24, p. 417) or prepare his apparatus (March 10, p. 525) for anaesthetizing the patient. What does he do with the few moments of time he saves? Surely the practice of a third party charging syringes for someone else to use will sooner or later lead to disaster which cannot be defended in law. The theatre technician is no more infallible than any other human being—accidents can happen to anyone.

Apart from the junior nurses who come to the theatre for 6–8 weeks' training in theatre principles, the theatre nursing staff is permanent and reliable enough to carry on the efficient running of any theatre without the surgeon or anaesthetist fearing that their patients will suffer. I devote part of my time to teaching students, and I am always prepared to allow junior theatre nurses to "scrub up" and put into practice the theory they have been so well taught. I can safely say that this consideration is always appreciated by the staff and rewarded by greater endeavour to improve. Give me the pleasant female nursing staff any time in preference to male. As I see it, there is no place in our operating theatres for a special class of technician to perform the duties mentioned in your annotation (January 13, p. 80), or in the subsequent letters referred to above, which cannot be done just as well by a good theatre porter. Where is all this clamour for extra non-medical assistants with diplomas going to end, and who is going to foot the bill?—I am, etc.,

Sheffield. DAVID AIKEN.

Syringe Needles and Mass Inoculation

SIR,—The article by Sir Alexander Fleming and Dr. A. C. Ogilvie on the subject of mass inoculation technique (March 17, p. 543) is a valuable contribution to the subject. I am glad that the authors included the information that immersion of the needle in boiling water for ten seconds proves an adequate guard against transmission of infection, taken in conjunction with other wise precautions. Most centres for mass inoculation have electric sterilizers (in which, by the way, the wise operator uses distilled water) whereas a convenient gas supply is often not available. Thus, the use of hot oil would necessitate the purchase of a fairly costly thermostatically controlled electric bath. A further point in favour of boiling water may be, I think, that the use of a temperature of 100° C. would be less likely to cause drying of the contents of the needle-bore, with consequent clogging, especially with materials containing an aluminium carrier, than would higher temperatures employed in the oil bath.

It goes without saying that all syringes and needles must have undergone a reliable primary sterilization by one of the accepted methods, of which prolonged boiling in distilled water is that usually employed in the ordinary inoculation clinic. Then, on the basis of the article, a sound routine for mass inoculation work should be

(*a*) The choice of a syringe of which the plunger is a real ground fit so that the danger of leakage up the side of the plunger during high-pressure injections (e.g., a Schick test) is virtually abolished.

(*b*) The use of a good quality of rustless needle, which will stand repeated insertion in boiling water.

(*c*) Drawing up of only the amount of fluid required for injection, keeping the plunger pressed firmly home after administration, until withdrawal from the body.

(*d*) Immersion of the needle to half-way up the boss, for ten seconds, in boiling water.

(*e*) Waiting for a second or two to cool the needle before recharging, at any rate when filling with Schick toxin, if only 0.2 ml. of this is being drawn up.

I calculate that the procedure outlined by the authors will take some eight seconds longer per case than does needle changing, but this is well worth while if it abolishes danger of cross-infections.—I am, etc.,

London, S.E.5. GUY BOUSFIELD.

Value of Pernasal Swabs

SIR,—I would like to comment on Dr. Stanley Banks's reference to the bacteriological diagnosis of whooping-cough in his valuable article (March 31, p. 689). He states that the pernasal swab is of value only "just after a paroxysm." Our experience in the course of following up large numbers of children in the M.R.C. pertussis vaccine trials in this city is that the pernasal swab (and its predecessor the post-nasal swab) is of great value in the diagnosis of the disease in the early stages, long before the paroxysmal phase has appeared. It is also valuable in the diagnosis of the very mild cases in which the cough never becomes paroxysmal at all. A recent instance of the importance of the pernasal swab was in a baby aged 2 months in a mother-and-baby hostel. He was known to have been exposed to infection, so when he developed mild catarrhal symptoms he was isolated and a swab was taken at once. The presence of *H. pertussis* was reported on the third day, and he was removed to a whooping-cough ward in hospital long before there was any paroxysmal cough.—I am, etc.,

Oxford. MARY FISHER.

Scotland Leads the Way

SIR,—In a leading article (March 17, p. 571) you state: "That the public is prepared to respond to an intelligent approach to (health education) was shown dramatically during the war, when the Ministry of Health under Sir Wilson Jameson secured such a widespread use of diphtheria prophylaxis that the morbidity and mortality of this disease fell sharply and dramatically over a period of four to five years." I have no reason to question that statement, but, for the sake of historical accuracy, I would like to have it recorded that the Department of Health for Scotland opened its preventive campaign against diphtheria in December, 1940, almost 12 months before the Ministry of Health began. Moreover, the dramatic fall in the incidence of, and mortality from, diphtheria occurred even more dramatically in Scotland. Deaths from diphtheria in 1940 amounted to no less than 676, but the annual figures have decreased continuously during the last 10 years until, during 1950, only three deaths from diphtheria were recorded. It may reasonably be claimed that this is one of the most striking successes which preventive medicine has ever achieved in this country.—I am, etc.,

Bridge of Allan, Stirling. A. J. H. RUSSELL,
Late Deputy Chief Medical Officer,
Department of Health for Scotland.

Medical Education in the U.S.A.

SIR,—I was very glad to read your annotation (March 17, p. 576). The radical experiment which the Commonwealth Fund is supporting at the Medical School of Western Reserve University has been made in order to correct the disconnected state of medical teaching in the separate departments of medical schools. This undesirable state was taken also as a starting point by the Medical Curriculum Committee of the B.M.A. in preparing their excellent report on medical education, published by Messrs. Butterworth, with the title *The Training of a Doctor*. The British report is of course advisory, in contrast to the actual experiment in Cleveland, but advice and experiment both aim at getting teachers to integrate their courses as much as possible, so that they know that each department contributes to the

object of teaching students the art of satisfying the needs of sick people. This art is based on a personal relationship of doctor and patient, and both the American and British studies of the subject lead to the conclusion that careful attention must be given to cultivating it. In the American experiment this is emphasized by a course in the first year called the "Introduction to Clinical Medicine," which is given by an internist long interested in "individualizing" the patient, a physical anthropologist interested in constitutional differences, a psychiatrist, and a social worker. In the British report the same aim is pursued throughout the course by teaching that the patient must be treated as an individual and as a whole.

It appears to me that sufficient facts and views have been collected in the British report for medical schools in this country to settle on their individual aim and to decide how much change they require to make. In Edinburgh very useful integration of lectures has been arranged by the departments of surgery, medicine, pathology, and therapeutics, and weekly demonstrations on diseases set out by these departments in combination.

I hope that you will be able to report interesting progress in the American experiment, and the commencement and development of similar enterprises in this country. The question is whether doctors are anxious to continue to direct the technical efforts of themselves and others towards the greatest possible benefit of the patient, or whether they are willing to become more absorbed in detailed medical technique. It is in hospitals that there is most risk of this narrower outlook, and if it becomes general doctors will lose some of the direction in medical affairs which they now have.—I am, etc.,

London, W.1. J. M. ALSTON.

Girls with Moustaches

SIR,—In "Any Questions?" (March 24, p. 652) there is a query about the best way of removing a small moustache from an otherwise normal girl of 15. The answer deals solely with methods of removal, and does not give suggestions about treatment, which in my opinion is most important. Brunettes, especially when there is a familial or racial darkness of hair, frequently show an exaggeration of hair growth on the upper lip at adolescence. These hairs may tend to coarsen in the next five to ten years or they may gradually become less noticeable. The only treatment needed in the early stages is tactful handling, combined with artificial bleaching in suitable cases. Ten volumes hydrogen peroxide made faintly alkaline with ammonia and applied as a compress for a few minutes daily and then carefully rinsed off is usually sufficient to camouflage the condition. If coarser hairs develop, electrolysis or diathermy will be the method of choice, and fairly coarse hairs are easier to treat than downy hairs.

Neuroses and feelings of inferiority and shame commonly start in adolescence when the hirsuties is first noticed, and sympathetic, though practical, handling of the problem is most necessary. The increased tendency since the war to the development of acne, together with earlier applications of face-creams and cosmetics and the greater popularity of sun-bathing, may contribute to some thickening of down hair into frank hirsuties. Endocrine factors as such probably play little part in the appearance of hirsuties in a girl of 15. Wax depilatories should be condemned for use by young girls, as both fine and coarse hair is pulled out when the cold-set wax is finally dragged off the face.

Rubbing with pumice and the use of chemical depilatories (barium sulphide) are both temporizing measures. Although the free growing ends of the hair appear again in due course, they are not sharp and "stubbly." This treatment has to be applied regularly, and the hairs will gradually coarsen and the area affected will tend to enlarge at the periphery. Manual depilation by plucking out coarse hairs has to be repeated every few weeks. The roots tend to coarsen, to elongate, and to become distorted. Later, if electrical treatment is started, difficulty will be experienced in killing the root with a safe current—that is, a current that will not also damage the skin.

There is need for a much better understanding of the problem of hirsuties, and how it affects the mental and emotional make-up of women. A careful consideration of the treatment to be suggested is most necessary.—I am, etc.,

Kew. CLARA M. WARREN.

POINTS FROM LETTERS

Artificial Lighting

Dr. G. LAWSON (London, E.2) writes: I have found, in common with other practitioners, that the bane of an evening surgery in winter time is a difficult rash almost impossible to diagnose in artificial light. Having considered the possibility of fluorescent lighting and finding this to be too expensive, I have discovered that an almost perfect colour reproduction is given by a daylight bulb. These 100-watt lamps can, with advantage, be used in conjunction with an ordinary 60-watt lamp, which softens the somewhat cold light derived from the daylight bulb alone, but can be switched off when a difficult problem arises.

Retrolental Fibroplasia

Mr. EUGENE WOLFF (London, W.1) writes: . . . In a paper (*Proc. R. Soc. Med.*, 1950, **43**, 235; *Amer. J. Ophthal.*, 1950, **33**, 1768) I pointed out that the most striking feature of the pathological picture of this interesting condition was the anterior end of the retinal detachment which usually accompanies the disease. This consists of the clear cells of the ciliary body, which normally unite very firmly with the underlying pigmented layer at about the third or fourth month of intrauterine life. . . . I also showed that the membrane behind the lens was in fact inflammatory and not the remains of embryonic tissue as generally supposed. Without going into further details, I would only like to repeat here the suggestions I made for the order of events. A noxious stimulus reaches the embryo very early, probably in the first few months of intrauterine life. Its effect on the eye is primarily on the retina, which remains non-attached in part or as a whole. (The noxious stimulus may affect other parts of the organism, especially the brain, as pointed out by Krause, hence his name for the disease, encephalo-ophthalmic dysplasia.) Fluid collects under the retina and a real detachment is produced which gradually becomes total. This may give rise to a mild uveitis, which is responsible for the retrolental membrane and the posterior synechiae, when these are present. It is therefore extremely unlikely that any post-natal treatment can be of much avail.

Absorption of Iron

Dr. E. LOZINSKI (Montreal, Canada) writes: Your leading article (February 3, p. 231) . . . recalled to me an almost forgotten study (S. J. Usher, P. N. MacDermot, and E. Lozinski, *Amer. J. Dis. Child.*, 1935, **49**, 642) in which it was shown that the administration of a soluble iron phosphate preparation was quite effective in improving the simple anaemia of infants. It would seem . . . that whatever may be the situation in experimental animals the amount of phosphate and calcium supplied by the dietary regime of these children was not a factor of consequence with respect to the assimilation of iron even from an iron phosphate compound.

A Vaccination Dressing

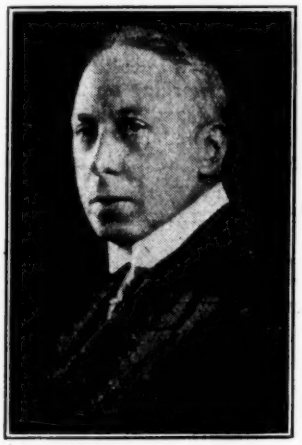
Dr. R. D. DEWAR (Deptford, S.E.14) writes: One of the difficulties encountered in vaccination against smallpox, especially when dealing with large numbers, is the delay occasioned by allowing the lymph to dry before a dressing is applied. The delay can be avoided by using as a dressing one half of a cachet, such as is in normal use for the internal administration of powders. This "cap" can be applied immediately after vaccination and secured in place with a small piece of adhesive plaster. It is sufficiently deep to prevent contact with the vaccination area, it is both cheaper and more convenient than other forms of dressing, and in addition it prevents those unsuccessful cases which are due to the application of a dressing before the lymph has dried. The dressing can be discarded within a few hours, after which no dressing is necessary, in my opinion, for at least the first few days. Normal-sized cachets (No. 2) cost about 10s. a thousand. I am indebted to Dr. W. W. King-Brown, of Peckham, for introducing this dressing to me. I understand that it is not a new idea, but I have not previously seen it reported and I believe it is not widely known.

Obituary

CHARLES RICHARD BOX, M.D., F.R.C.P. F.R.C.S.

Dr. Charles R. Box, consulting physician to St. Thomas's Hospital and the Royal Masonic Hospital, died in St. Thomas's Hospital on April 3, aged 85 years.

Charles Richard Box was born in 1866. After leaving Dulwich College he started work in the City. But he very soon gave up the idea of a business career, and in 1884 entered St. Thomas's Hospital Medical School. He had a brilliant student career, which he crowned by securing a large number of qualifications. After taking the B.Sc. of London University in 1889, with honours in physiology, he qualified in 1891 and graduated M.B., B.S. the following year, with honours in medicine and obstetric medicine. He held the posts of house-physician and house-surgeon at St. Thomas's, and in 1893 he proceeded M.D. and also became a Fellow of the Royal College of Surgeons. After obtaining this surgical qualification Box devoted all his attention to medicine, obtaining the M.R.C.P. in 1897 and becoming a Fellow in 1906.



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At St. Thomas's, as at most hospitals until recent times, there was only one medical registrar, and Box held this appointment from 1894 to 1897, when he became resident assistant physician, a post which he held for three years before being elected to the staff as physician to out-patients. In due course he became full physician and physician-in-charge of the children's department. During the first world war he was appointed brevet major in the R.A.M.C.(T.) attached to the 5th London General Hospital. He retired in 1926 at the age of 60, and was made a consulting physician. In the medical school he was a lecturer in medicine and applied anatomy, and for a time was sub-dean. He also presided at the medical and surgical officers' committee. For years he conducted most of the post-mortem examinations and produced very full and most valuable reports on all of them. His very extensive knowledge of clinical medicine was based on meticulous observation of morbid processes. Besides serving St. Thomas's with all his energy, Box was also physician to the London Fever Hospital, the Royal Masonic Hospital, and the Willesden General Hospital. In the College of Physicians he was Censor from 1930 to 1931 and Lumleian Lecturer in 1933, his subject being the "Complications of the Specific Fevers." He was an examiner in medicine in the universities of Birmingham and London and to the Conjoint Board and Society of Apothecaries. A member of the Court of Assistants of the Society of Apothecaries, he was unable to accept the office of Master of the Court during the war, as he was then living in Devonshire. Box wrote only when some useful purpose was to be achieved. He was the author of the section on infectious fevers in Price's *Textbook of Medicine* and of a *Post-mortem Manual* published in 1910. He also collaborated with Mr. W. McAdam Eccles in writing a handbook entitled *Clinical Applied Anatomy*.

Box was a great clinician and had a most exceptional knowledge of medical literature; he could give chapter and verse to anyone inquiring about some obscure case. He was considered by many to be one of the greatest physicians of his time in London, but, as is not uncommon with consulting physicians, he never became a popular consultant, in spite of his great attainments, though he was called in by a large number of doctors when they were in difficulties with some obscure case. He was perhaps not an easy man to know, yet those who worked with him in hospital and at the Society of Apothecaries, and met him at masonic meetings, did get to know him well and valued his friendship, loyalty, and kindness of heart.—J. P. H.

J. O. SYMES, M.D.

Dr. J. O. Symes died at his home in Clifton, Bristol, on March 24 at the age of 83.

John Odery Symes was born in Taunton and received his medical education at University College and St. Mary's Hospital, London. He qualified in 1891, graduated M.B. with honours in medicine two years later, and proceeded M.D. in 1895. After holding resident appointments at St. Mary's and the London Fever Hospital he came to Bristol, and in 1897 was appointed honorary bacteriologist to the Royal Infirmary when the bacteriological department was first opened. Two years later he moved to the Bristol General Hospital as assistant physician and continued to serve on the honorary medical staff of that institution with complete devotion for some 28 years until his retirement in 1927. He was a lecturer in clinical medicine at the University for a number of years. After his retirement from the Bristol General Hospital he continued in private practice until a few years ago. He expressed his continued attachment to the hospital by writing a history to mark its centenary in 1932. His wide interests included the presidency of the Anchor Society and chairmanship of Badminton School for girls, of the Bristol Medico-Chirurgical Society, and of the Bath and Bristol Branch of the B.M.A. At one time he was physician to Clifton College. Symes was an outstanding example of the physician who combined in full measure the role of consultant and family doctor. Wise, scientific, and a great judge of human nature, his help was valued in equal measure by his own patients and by his colleagues in consultation, which is evidence of the very high standard of his professional behaviour. Apart from his professional services, his friendship was valued and freely given to patient and fellow practitioner. He led a full and most valuable life.—A. J. W.

Dr. D. S. McCONNACH was killed in a climbing accident on Beinn a'Bhuird in the Cairngorms on March 11. He was only 22 years of age. Donald Simpson McConnach was born in Aberdeen and educated at Aberdeen Grammar School, which he left in 1945 when he entered Aberdeen University. As a student he was a popular member of his year and earned the love and respect of his colleagues. He had an active inquiring mind and a fine sense of humour. Graduating M.B., Ch.B. last September, he was working as a house-physician in the Aberdeen Royal Infirmary at the time of his

death. His thoughtfulness and self-sacrifice, combined with his cheerful manner and ability to perform hard work, marked him as one who had much to live for in his chosen profession. All through his short career Donald McConnach took an active interest in many and varied pursuits. He was of athletic build, taking naturally to sports of all kinds. From mountaineering he gained most pleasure. A keen and experienced climber, his company was sought by many in Aberdeen and elsewhere. He loved the Scottish Highlands and spent much of his available free time in learning to know them intimately. His tragic death is mourned by many, and deep sympathy will be extended to his mother and sister, who only two months previously lost Donald's elder brother suddenly in Africa.—I. M. B. and A. D. L.

I. G. writes: Donald McConnach joined the Cairngorm Club before he left school and was an active member for seven years. Latterly he had become a fully trained and experienced mountaineer. As a student in the wards of the Royal Infirmary he showed much ability and a capacity for hard work, which earned for him the post of house-physician in September of last year. Though small in stature, he was robust, and the spirit of adventure was translated into energy and enterprise in his daily duties. He worked without sparing himself not only in the treatment of his patients but also to improve and extend his own knowledge. To his work he brought kindness, understanding, and sympathy, without which the practice of medicine loses so much of its value. All these qualities earned for him our love and confidence and a popularity with his fellows which few can hope to attain. Like many fine young men he was simple in his tastes and modest almost to a point of diffidence. We shall not forget the twinkle in his eye, his happy laugh, and his bright outlook on life. Donald McConnach will be sadly missed and his memory will be cherished by all those fortunate enough to have known him.

Dr. CECIL BERRY, who had a long and varied career in tuberculosis, died at his home in Lathom, Lancs, on March 13 at the age of 66. The son of a general practitioner who was (in those days) part-time M.O.H. of Wigan, he qualified at Edinburgh in 1907 and took the D.P.H. in Ireland in 1911. After a year at the Birkenhead Children's Hospital, he joined the family practice in Wigan, and then in 1910 he took a special course of instruction in tuberculosis at Liverpool. In 1913 he entered the public health service as assistant tuberculosis officer for Stoke-on-Trent, and he moved to a similar post in Oldham in 1915. In 1919 he became a district tuberculosis officer in Durham. During the first world war he served in the R.A.M.C. as a regimental M.O. in France. In 1920 he began his long service with the Lancashire County Council as an assistant T.O. for the Ashton-under-Lyne district. About eight years ago he was promoted to a senior post, taking charge of the S.W. Lancashire area centred on Waterloo, with branch dispensaries at Huyton, Widnes, and St. Helens, and a 50–60-bed hospital for pulmonary tuberculosis at Rufford. When the National Health Service was established he was transferred to the staff of the Liverpool Regional Hospital Board, and he retained the same duties, with a little reorganization, until retirement in November, 1950. For a short time thereafter he took temporary duty in the Manchester region at Eccles and Salford to give help during a staff shortage. A loyal, genial, generous, and likeable man, but over-diffident about his own attainments, he gave solid and thorough service as one of the old County Palatine tuberculosis team, and, last but not least, he excelled in giving encouragement to younger colleagues. Our sympathy is extended to his widow. —G. L. C.

By the death of Dr. W. H. OWLES on March 20, at the age of 44, North Wales has lost one of its most brilliant younger physicians. Wilfred Harding Owles was a Londoner by birth, and from St. Paul's School he gained a scholarship to Exeter College, Oxford, where he had a brilliant undergraduate career. He obtained first-class honours in physiology in 1928, and graduated B.Sc. with honours in 1929. Continuing his medical studies at Guy's Hospital, he graduated B.M., B.Chir. in 1932. Owles published a number of papers during his lifetime, including contributions to the *Journal of Physiology* before he qualified. He was particularly interested in the physiology of digestion. After holding resident appointments at Guy's, including that of neurological house-physician, he became a medical registrar at Queen's Hospital, Birmingham. In 1934 he took the M.R.C.P. and was elected to a Rockefeller travelling fellowship and research fellowship in medicine at Harvard University. On his return to this country he proceeded D.M., and in 1938 went to Llandudno as a partner in a well-established practice. During the war years he carried on this practice alone, for he was himself unfit for service, and this work took a great toll of his health. When the National Health Service was established in 1948 Owles decided that his future lay in consultant practice, and he became a full-time consultant in medicine on the staff of the Llandudno and District Hospital and the Caernarvon and Anglesey Infirmary at Bangor. About two years ago he had a serious breakdown in health, and no one realized better than he that he had only a short time to live. However, he fought on against adversity and ill-health with a dogged determination, and was actually working on the day of his death. He was greatly respected and liked by his patients, and his opinion was highly valued by doctors in the area. The sympathy of his colleagues at this time goes out to his wife and three young children.—C. C.

Medico-Legal

CERTIFICATION OF MENTAL PATIENTS

[FROM OUR MEDICO-LEGAL CORRESPONDENT]

A perennial source of anxiety to doctors is that they may have actions for damages brought against them by patients who upon their certificates have had reception orders made against them and have been detained in mental hospitals. Their anxiety is justifiable. As the late Dr. Stallybrass said in his tenth edition of *Salmond on the Law of Torts*, "The courts have been caused much trouble in connexion with medical certificates upon which reception orders are made." His conclusion after a close examination of the cases of *Everett* v. *Griffiths*[1] and *Harnett* v. *Bond*[2] was that in English law it is the doctor's certificate which is the effective cause of the detention, and not the act of the authority who makes the order. In the case of *Harnett* v. *Bond* damages amounting to £25,000 in all had been awarded by the jury, though the Court of Appeal reversed this result and their judgment was affirmed by the House of Lords. Such actions can be serious.

The doctor's duty, both in English and in Irish law, towards his patient in making his certificate is the same as his duty in his treatment of any other patient—namely, to act in good faith and to exercise reasonable care. Parliament, however, realizing the risk of such actions by patients who have suffered detention to be very real, and appreciating that even an unsuccessful action is likely to cause serious harm as well as expense, has given the doctor special protection. Section 16 of the Mental Treatment Act, 1930, expressly provides that where a doctor has signed, or done any act with a view to signing, a certificate purporting to be a certificate under the lunacy legislation, he shall not be liable in any proceedings unless he has acted in bad faith or without reasonable care, and no proceedings may be brought against him without leave of a High Court judge. The doctor is entitled to oppose any application for leave, and the judge must not give leave unless he is satisfied that

[1] 1921 A.C. 631.
[2] 1925 A.C. 669.
[3] *Irish Times*, February 24.

there is substantial ground for the contention that the doctor has acted in bad faith or without reasonable care.

The result of this provision is that no such action is allowed to be started, with all the attendant publicity and expense, unless it has a real prospect of success in the eyes of a High Court judge.

In a recent action in the Dublin High Court[1] the jury awarded £980 damages against Dr. James A. Lynch, of Stamullen, County Meath, in an action brought against him by Mr. William McDowell, a 59-year-old farmer of Stamullen. Mr. McDowell was committed to Mullingar Mental Hospital on June 20, 1948, on Dr. Lynch's certificate, and after an inquiry, in which he was found to be sane, was released on March 11, 1949. Mr. McDowell alleged both bad faith and want of reasonable care against Dr. Lynch.

In his summing up to the jury at the close of the eight-day trial Mr. Justice Dixon observed that there is no legal definition of "bad faith," but it included improper motives, dishonesty, and deliberate disregard of Dr. Lynch's duty and Mr. McDowell's rights. All these matters might be combined in the proposition whether Dr. Lynch had a state of mind actively hostile to Mr. McDowell or that he intended to cause him injury or was recklessly indifferent whether he did or not. Dr. Lynch had never carried out the usual mental examination of Mr. McDowell. On the day on which the certificate had been given Dr. Lynch had said he could not examine Mr. McDowell because he had run away and it was not his business to follow him. The jury might think this was a rather casual way of dealing with such an important matter.

On the question of reasonable care, the jury had to decide whether the doctor had exhibited the standard of reasonable care they would expect from a person in his position in a matter of this kind. He had certified that he had "on this day" examined the patient, which was untrue, and so misleading. Mr. Justice Dixon then dealt with the doctor's evidence of the reasons for which he had decided to give his certificate. In fairness to the doctor the jury had to take into consideration his own previous knowledge of the patient and his history, the fact that he knew that Mr. McDowell had previously been confined in the Stewart Institution as a certified patient, and the fact that the medical superintendent of that institution and the medical superintendent of St. Patrick's Hospital, Dublin, had reported in November, 1947, that there was a risk that, if Mr. McDowell returned to live in the same house as his wife without a third party present, he would do her grievous bodily harm.

The jury found that Dr. Lynch had acted without reasonable care, and disagreed on the question of bad faith.

Universities and Colleges

UNIVERSITY OF ST. ANDREWS

At a graduation ceremony to be held on June 29 the honorary degree of LL.D. will be conferred on the Rt. Hon. Walter Elliot, P.C., M.B., F.R.C.P., F.R.S., and on James Lawson, M.D., M.R.C.P.Ed., Assessor of the General Council on the University Court of the University of St. Andrews.

UNIVERSITY OF LONDON

The following candidates have been approved at the examination indicated:

ACADEMIC POSTGRADUATE DIPLOMA IN MEDICAL RADIOLOGY (THERAPY).—*Part I:* K. A. Newton, R. C. S. Pointon, L. C. Robson, Jean K. M. C. Wilson.

UNIVERSITY OF WALES

Professor A. G. Watkins, recently appointed Professor of Child Health in the Welsh National School of Medicine, will deliver an inaugural address on "Child Health" in the Reardon Smith Lecture Theatre, Park Place, Cardiff, on Thursday, April 26, at 8 p.m.

UNIVERSITY OF BIRMINGHAM

The Council of the University has conferred on Dr. J. F. Brailsford the title of Emeritus Director of Radiological Studies in the Living Anatomy in recognition of the valuable services he has rendered to the University.

UNIVERSITY OF LIVERPOOL

The following candidates have been approved at the examinations indicated:

FINAL M.B., CH.B.—*Part II:* Gwerfyl Alun-Roberts, Ursula M. Anderson, Margaret M. Ashcroft, A. C. Beeby, F. Berry, A. S. Binnie, J. S. Birch, Elizabeth Bownass, Margaret T. Brash, N. H. Brodie, J. M. Brown, J. W. Brown, T. Bury, E. P. Carrigan, D. A. P. Cooke, W. E. Cooper, G. Corney, Enid C Davies, J. C. Denmark, A. J. Entwistle, R. J. Fallon, R. H. Fitzgerald, W. D. Fitzsimons, B. Freeman, Mary I. Gibbons, A. E. Goetzee, L. V. Gould, K. Grainger, P. W. Green, L. A. Guile, F. B. Hartley, N. St. J. Hennessey, Barbara M. Hitch, J. Hogan, J. Hosker, Eileen M. Howarth, E. M. Hughes, G. Ingram, Irene M. Irving (with distinction), Brenda Jones, R. D. Jones, Winifred E. Jones, Joan Knowles, P. P. Kudernatsch, W. G. Lamberd, A. M. Laylee, D. G. G. McLeish, I. Miller, Maureen E. Murphy, L. A. Nettleton, A. Nixon, G. Park, W. G. W. Parry, F. P. Peach, E. J. Raffle, V. Rogers, H. G. Row, A. Sandieson, A. C. Saunders, S. J. Surtees, T. E. Tasker, T. D. Thomas, P. G. Vivian, E. S. Watkins, W. A. Weston, N. Wignall, A. H. Wilde, D. W. B. Woolven (with distinction), J. D. Wright, P. H. Wright, Madge Yates.

DIPLOMA IN RADIOLOGY (RADIODIAGNOSIS).—*Part I:* F. G. Anderson, W. E. C. Astle, E. Walker, J. K. Walker.

UNIVERSITY OF LEEDS

Robert Sutherland, M.D., D.P.H., has been appointed Senior Lecturer in Preventive Medicine and Public Health. Dr. Sutherland has been medical adviser and secretary to the Central Council for Health Education for the past eight years and editor of the *Health Education Journal* for over eight years, having been associated with the editorship from the first issue. He is a member of the Colonial Advisory Medical Committee and was a member of the Ministry of Food Catering Trade Working Party, the report of which was reviewed in the *British Medical Journal* of February 17 (p. 345).

Maurice John Parsonage, M.B., Ch.B., M.R.C.P., D.C.H., Assistant Physician to the United Leeds Hospitals, has been appointed Clinical Lecturer in the Department of Neurology.

The Council of the University has approved a recommendation for the institution of a part-time course leading to the award of the Diploma in Public Health.

ROYAL COLLEGE OF SURGEONS OF ENGLAND

The Lister Medal for 1951 has been granted to Sir James Learmonth in recognition of his distinguished contributions to surgical science. Sir James Learmonth will deliver the Lister Memorial Lecture in London on April 4, 1952, under the auspices of the Royal College of Surgeons of England. This is the tenth occasion of the award, which is made by a committee representative of the Royal Society, the Royal College of Surgeons of England, the Royal College of Surgeons in Ireland, the University of Edinburgh, and the University of Glasgow.

ROYAL COLLEGE OF PHYSICIANS OF EDINBURGH

At a quarterly meeting of the College held on February 6, with Sir David K. Henderson in the chair, the following were elected Fellows of the College: Y. A. Sherif, F. S. Airey, G. D. F. Steele, J. W. Buchanan.

The following were elected Members of the College: V. T. H. Gunaratne, R. J. Grove-White, Agnes L. Scott, P. N. Laha, K. Damodaran, B. N. Fraser, R. K. Richardson, G. S. El-Assal, H. Chai, A. C. A. Coombes, J. U. Crichton, E. H. Taft, Yee Ip, Mary M. M. Boyd, Sylvia Goldberg, Hing Yiu Mok, D. L. Gardner.

ROYAL FACULTY OF PHYSICIANS AND SURGEONS OF GLASGOW

At a meeting of the Faculty held on April 2, with the President, Mr. Walter W. Galbraith, in the chair, the following candidates were admitted Fellows of Faculty *qua* Physician: W. D. H. Conacher, A. Goldberg, P. G. Griffiths. The following candidate was admitted a Fellow of Faculty *qua* Surgeon: I. A. McGregor.

Vital Statistics

Poliomyelitis

In the week ending March 31 notifications of poliomyelitis were as follows: paralytic, 19 (10); non-paralytic, 4 (3); total, 23 (13). The figures for the previous week are in parentheses.

Total uncorrected notifications for the first 13 weeks of the following years have been as follows: 1947, 125; 1948, 418; 1949, 248; 1950, 512; 1951, 337.

Biostatistics in Lancashire

In his Annual Report for the year 1949, Dr. Alan S. Simpson, Divisional Medical Officer for Lancashire County Council, analyses some data on the birth and feeding of babies. He found that 1,215 baby boys had a mean weight of 7 lb. 6¼ oz., while the mean weight of 1,124 baby girls was 7 lb. 4 oz. The difference is statistically significant. Variation in weight was slightly greater among male than female infants.

In 219 cases estimates of the expected date of delivery were checked against the actual date of delivery. In 7 cases (3%) the two dates coincided; in 44 cases (20%) delivery was one to seven days before the expected date; and in 50 cases (23%) it was one to seven days after the expected date. In other words, only about half the deliveries were within a fortnight of the expected date.

He carried out an inquiry among 876 children who had attained their first birthday to find out how long they had been breast-fed. His results are shown in the following Table:

	No.	%
Weaned between birth and 1 month ..	379	43
,, ,, 1 month and 3 months	202	23
,, ,, 3 months and 6 months	207	24
Not weaned before 6 months	88	10
Total	876	100%

Tuberculosis in Scotland

The following Table, taken from the Report of the Department of Health for Scotland for 1950, shows, for tuberculosis, the notifications, deaths, and death rates per 100,000 population.

Year	Respiratory			Non-respiratory		
	Notifications	Deaths	Death Rate per 100,000 of Population	Notifications	Deaths	Death Rate per 100,000 of Population
Average 1913–17	9,146	5,102	107	4,659*	2,661	56
,, 1918–22	7,870	4,347	90	4,351	1,977	41
,, 1923–7	6,771	3,693	76	4,900	1,619	33
,, 1928–32	5,831	3,125	64	4,205	1,258	26
,, 1933–7	4,950	2,816	57	3,025	901	18
1938	4,793	2,581	52	2,772	851	17
1939	4,657	2,717	54	2,440	809	16
1940	5,212	3,018	62	2,510	961	19
1941	5,739	3,117	63	2,555	1,058	21
1942	6,224	3,043	62	2,824	955	20
1943	7,215	2,976	62	2,873	983	21
1944	7,282	2,978	62	2,651	958	20
1945	7,316	2,932	60	2,342	871	18
1946	7,627	3,231	64	2,086	753	15
1947	7,984	3,390	66	2,133	705	14
1948	8,204	3,415	66	1,842	486	9
1949	8,653	3,084	60	1,647	400	8
1950	8,138†	2,443	47	1,544†	336	6

* Non-respiratory tuberculosis notifiable only from July 1, 1914.
† Provisional.

Quarterly Report for Scotland

The birth rate during the fourth quarter of 1950 was 16.8 per 1,000 of the population and was 2.0 below the average of the five preceding December quarters; it was the lowest rate experienced in Scotland in any quarter since 1945. The infant mortality rate was 42 per 1,000 live births and was 2 below the rate for the fourth quarter of 1949. The death rate was 13.1 per 1,000 of the population and was 0.9 above the average of the five preceding December quarters.

The death rate from respiratory tuberculosis was 46 per 100,000, and 51 from all forms of tuberculosis. These rates were 11 and 12 respectively below the rates for the corresponding quarter of 1949.

Deaths for the year 1950 attributed to the principal infectious diseases numbered 527, 45 fewer than in 1949. The deaths from infectious diseases included 386 from influenza, 61 from whooping-cough, 38 from measles, 35 from cerebrospinal fever. Only 3 deaths were due to diphtheria, and this was the lowest number ever registered in Scotland. Deaths from acute poliomyelitis and acute encephalitis numbered 63, an increase of 51 on the previous year, but in 1947 the number of deaths under this heading was 129. The number of deaths from heart disease was 20,300, and was the largest number ever recorded; these deaths formed 32% of all deaths. (Other Scottish statistics for 1950 were given in the *Journal* of April 7, p. 756.)

Anthrax in Animals and Fowl Pest

In the period January 1 to March 15 of this year 135 cases of anthrax in animals were notified. The figures for the corresponding period in the previous years are as follows: 1950, 112; 1949, 34; 1948, 26.

In the same period there were 428 confirmed outbreaks of fowl pest. The figures for the corresponding period in the previous years were: 1950, 36; 1949, 101; 1948, 129.

Smallpox and Typhus in Korea

Smallpox and typhus are prevalent in North Korea, according to a report received on March 17 by W.H.O. from Tokyo (W.H.O. *Weekly Epidemiological Record*, April 4). Sporadic cases of these diseases have also been reported from South Korea.

Births, Marriages, and Deaths in 1950

In England and Wales in 1950, according to the Registrar-General's *Quarterly Return* for the quarter ending December 31, 1950, the provisional birth rate per 1,000 population was 15.8. This was 0.9 below that for 1949. The illegitimacy rate was 49 per 1,000 live births, which was 15 per 1,000 below the average for the preceding five years.

The provisional stillbirth rate was 22.6 per 1,000 total births—0.1 below the figure for 1949. The general death rate was 11.6 per 1,000—0.1 below that for 1949. The infant mortality rate was 29.8 per 1,000 related live births; it was the lowest ever recorded in this country and was 2.4 per 1,000 below the rate for 1949.

The births registered exceeded the deaths by 182,148; the corresponding increase for the preceding year was 210,479, and the average for 1944–8 was 290,783. Births in 1950 were 2% below the number required by a par replacement standard. The marriage rate of 16.3 was 0.8 below that of 1949.

The Registrar-General has also issued his *Estimates of the Population of England and Wales* as at June 30, 1950 (H.M.S.O., 6d.).

Population in the U.S.A.

The population of the U.S.A. is 6½ times what it was a century ago, having increased from 23 million in 1850 to 151 million in 1950 (*Statistical Bulletin*, Metropolitan Life Insurance Company, February, 1951). The rate of growth has been slowing down in recent years, though over the last 50 years the population has doubled. Rates of increase have varied markedly from one region of the country to another. The most rapid rate of growth has been in the west; it reflects the large-scale westward migration which began in the middle of the nineteenth century and is still continuing. Even in the decade between the two censuses of 1940 and 1950 the population increased 45% in Nevada, 50% in Arizona, and 53% in California.

Week Ending March 31

The notifications of infectious diseases in England and Wales during the week included: scarlet fever 918, whooping-cough 4,098, diphtheria 46, measles 31,268, acute pneumonia 909, acute poliomyelitis 23, dysentery 999, paratyphoid fever 21, typhoid fever 7. Deaths from influenza in the great towns numbered 64.

Infectious Diseases

During the week ending March 24 large decreases were recorded in the incidence of infectious diseases in England and Wales. The largest falls in the number of notifications were measles 4,024, whooping-cough 1,437, dysentery 416, acute pneumonia 170, and scarlet fever 88.

The decline in the incidence of measles was greater in the southern section of the country than in the northern. The largest falls in the number of notifications were Southampton 661, London 618, Lancashire 440, Essex 297, Cheshire 278, Middlesex 271, Kent 228, Surrey 227, while the chief exceptions to a declining incidence were rises in Somerset 134 and Sussex 82.

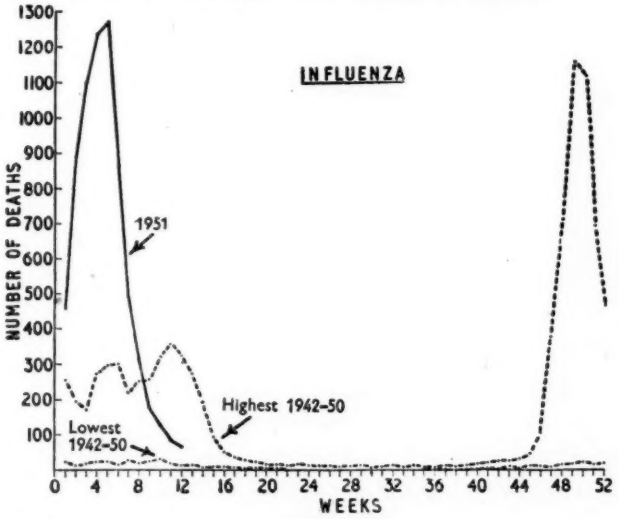
A decline in the incidence of whooping-cough was general throughout the country, although the largest fall was centred on London and the adjacent counties. The largest decreases were Kent 168, Lancashire 145, London 142, Essex 132, Surrey 102.

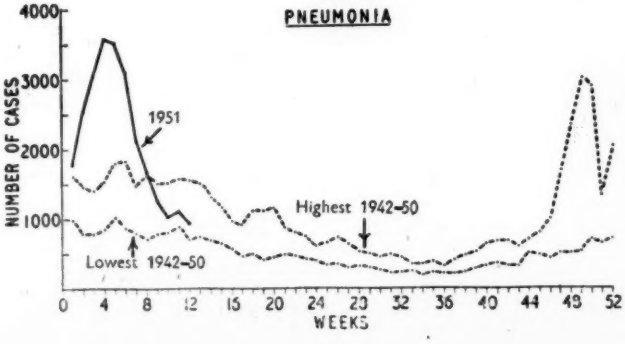
Only small variations occurred in the local trends of scarlet fever, with the exception of a fall of 30 in Lancashire. The number of notifications of diphtheria was the same as in the preceding week, and no variations of any size occurred in the incidence in any area. Of the 7 cases of typhoid fever 5 were notified in Sussex, Hailsham R.D. The only counties with more than one notification of acute poliomyelitis were Norfolk 3, Cheshire 2, London 2.

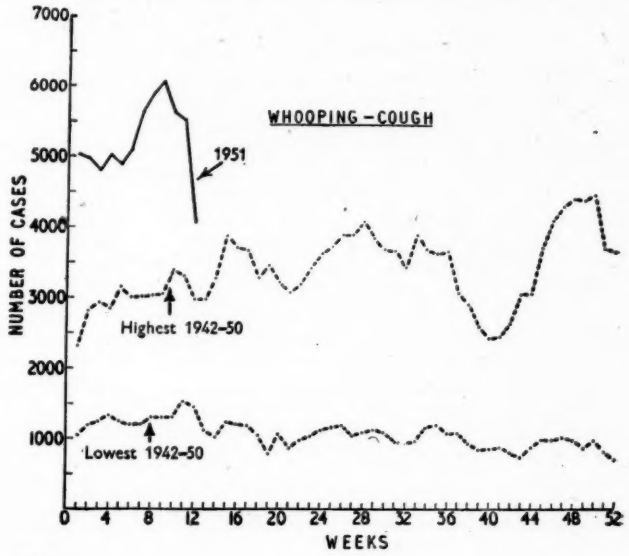
Despite the large fall in the number of notifications of dysentery the incidence remained very high, the largest centres of infection during the week being London 157, Lancashire 150, Middlesex 135, and Yorkshire West Riding 116.

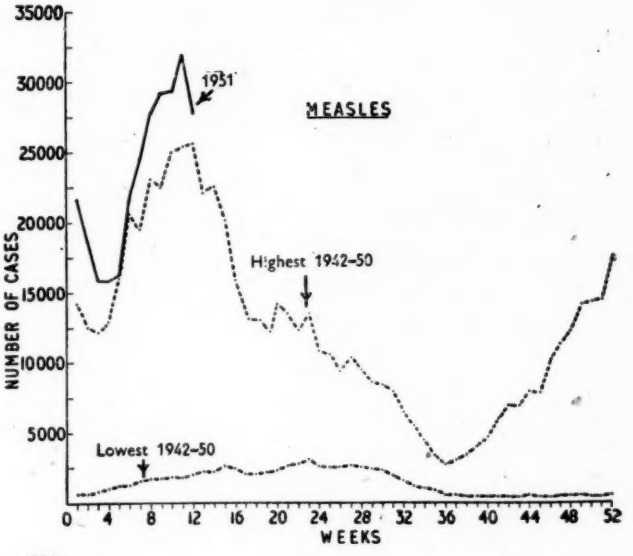
Graphs of Infectious Diseases

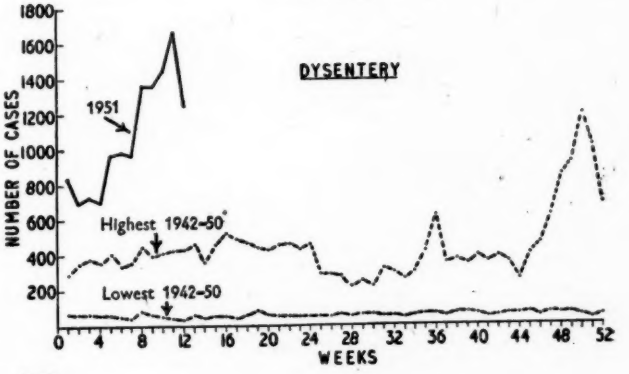
The graphs below show the uncorrected numbers of cases (deaths from influenza) of certain diseases notified weekly in England and Wales. Highest and lowest figures reported during the nine years 1942–50 are shown thus -------, the figures for 1951 thus ————. Except for the curves showing notifications in 1951, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.

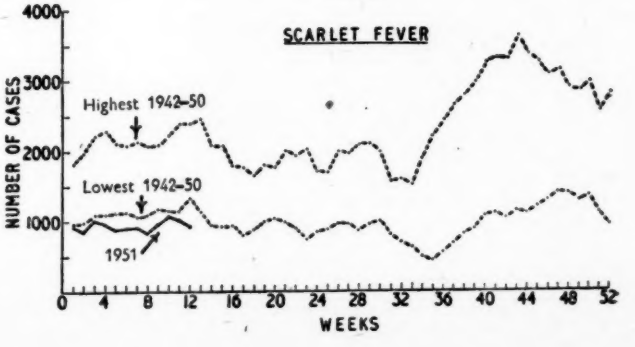












INFECTIOUS DISEASES AND VITAL STATISTICS

We print below a summary of Infectious Diseases and Vital Statistics in the British Isles for the week ending March 24 (No. 12).

Figures of notified *cases* are for: (*a*) England and Wales (London included). (*b*) London (administrative county). (*c*) Scotland. (*d*) Northern Ireland. (*e*) Eire. Figures of *births and deaths* and of *deaths* recorded under each disease are for: (*a*) The 126 great towns in England and Wales (London included), (*b*) London (administrative county). (*c*) The 16 principal towns in Scotland. (*d*) The 10 principal towns in Northern Ireland. (*e*) The 13 principal towns in Eire. A dash — denotes no cases; a blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, Northern Ireland, and Eire, the Ministry of Health and Local Government of Northern Ireland, and the Department of Health of Eire.

Disease	1951 Week Ending March 24					1950 Corresponding Week					1942–50 England & Wales Corresponding Week		
	(*a*)	(*b*)	(*c*)	(*d*)	(*e*)	(*a*)	(*b*)	(*c*)	(*d*)	(*e*)	Highest	Median	Lowest
Diphtheria	50	4	9	—	1	76	9	25	—	—	892	417	76
Deaths	—	—	—	—	—	—	—	—	—	—			
Dysentery	1,256	157	207	14		427	19	69	—	2	427	136	34
Deaths		1		—					—				
Encephalitis, acute	7	2	—	—		5	—	—	—	1	6	1	—
Deaths		—			—		—			—			
Erysipelas			19	—	4			22	2	8			
Food-poisoning	45	2		—		65	6		—				
Infective enteritis or diarrhoea under 2 years				15	19					11			
Deaths	14		1	1	2	16		3	—	2			
Measles*	27,813	2,518	428	114	85	5,716	98	329	404	95	25,507	9,308	1,875
Deaths		2	—	—	—			1	—	—			
Meningococcal infection	39	3	18	1	1	52	2	18	2	2	197	88	39
Deaths		1	1				—	—					
Ophthalmia neonatorum	34	—	8	—		37	5	12	—	1	105	67	37
Pneumonia, influenzal	936	50	13	8	12	1,082	53	13	24		1,547	1,082	720
Deaths (from influenza)†	67	6	3	—	5	135	15	4	6	9			
Pneumonia, primary			207					191					
Deaths	304	52		12	19	341	56		11	18			
Poliomyelitis, acute:													
Paralytic	10	2	—	—	—	29	3	—	1	2	29	9	4
Non-paralytic	3	—											
Deaths§	—	—			—	3	—			—			
Puerperal fever			5				—	13					
Puerperal pyrexia‖	65	7	6	1		116	13	8	1	—	191	169	99
Scarlet fever	919	66	124	41	70	1,805	112	222	115	64	2,389	1,522	1,311
Deaths		—	—	—	—			—	—	—			
Smallpox	—	—	—	—		—	—	—	—				
Deaths				—					—				
(1) Tuberculosis, respiratory			149	26				178	44				
(2) Tuberculosis, non-respiratory			21	4				31	8				
(1) Deaths	163	25	30	6	16	188	33	29	6	11			
(2) Deaths		6	5	2	3		3	3	2	5			
Typhoid fever	7	—	1	—	2	4	1	1	—	1			
Deaths¶	—	—	—	—		—	—	—	—		15	10	5
Paratyphoid fever	10	—	2 (B)	—		1	1	—	—				
Whooping-cough	4,079	260	641	21	48	2,362	93	398	51	71	2,978	2,244	1,453
Deaths	5	1	3	—	—	8	—	—	1	2			
Deaths (0–1 year)	282	26	30	17	27	243	28	40	15	27	574	387	244
Deaths (excluding stillbirths)	5,928	920	719	169	222	5,810	926	640	155	276	6,773	5,500	4,704
Annual death rate (per 1,000 persons living)			14·5					12·9					
Live births	6,756	1,085	843	234	387	8,177	1,261	976	234	444	10,583	7,663	6,366
Annual rate per 1,000 persons living			17·0					19·6					
Stillbirths	207	35	27			183	30	29			272	245	183
Rate per 1,000 total births (including stillborn)			31					29					

* Measles not notifiable in Scotland and returns are approximate. † Includes primary form for England and Wales, London, and N. Ireland. § The number of deaths from poliomyelitis and polio-encephalitis for England and Wales, and London (administrative county), are combined. ‖ Includes puerperal fever for England and Wales and for Eire. ¶ Deaths from paratyphoid fever are combined with those from typhoid fever.

Medical News

Shortage of Sulphur

The shortage of sulphur is likely to cause difficulty in the manufacture of a wide range of medical supplies. The Ministry of Health has stated:

"Every effort will be made to maintain supplies at as high a level as possible to meet medical needs, but it is essential, if shortages of vital products are to be avoided, that every economy (consistent with the needs of their patients) should be exercised by doctors both in hospitals and in the general-practitioner service in the ordering or prescription of all substances where sulphur or sulphuric acid are used during manufacture."

Sulphuric acid is needed for the production of antibiotics, aspirin, barbiturates, citrates, salicylates, hormones, and vitamins, and in addition many well-known drugs contain the element. Supplies of dressings and photographic hypo may also be affected.

The British Pharmaceutical Industry

The Association of British Pharmaceutical Industry welcomed Mr. H. A. Marquand, Minister of Health, as guest of honour at its annual dinner in the Dorchester Hotel on April 4. Proposing the toast to the pharmaceutical industry, Mr. Marquand spoke of his profound belief in the principle of joint consultation. He referred to the great increase in the production of drugs in recent years. Exports were now six times what they were in 1938—sales were particularly good in the dollar area—and manufacture of drugs for home consumption had also increased threefold. At the same time prices of some important groups of drugs—for example, the sulphonamides and antibiotics—were falling. He had himself had some experience of penicillin as a patient: a good exercise for a politician in learning to turn the other cheek. The industry had shown itself well able to meet emergencies. Last January, for instance, during the influenza epidemic, 28,500,000 prescriptions were dispensed, compared with the normal monthly rate of 18,000,000. Mr. Marquand congratulated the pharmaceutical industry on the valuable research work it had promoted. The three problems which he and the industry had to face were shortage of essential raw materials, the rise in the cost of drugs in the N.H.S., and waste. In his reply Mr. J. C. Hanbury, the president of the association, briefly reviewed the history of the pharmaceutical industry, on which, he believed, rested the initiative to develop new drugs and therapeutic substances. The health of the guests was proposed by Mr. E. G. Gross. Sir Henry Cohen's felicitously phrased reply contained some wise words on the cost of prescribing. What the patient needed he must, within the economic structure of the country, obtain. But would the economic structure sustain an annual bill of £112,000,000 for cortisone, assuming that there were 250,000 arthritic patients who might benefit from treatment? Efforts must be made to ascertain the least costly drugs for the purpose intended, and more thought should be given to the avoidance of possible abuses of the N.H.S.

Birmingham and Midland Obstetrical and Gynaecological Society

At the spring meeting of the Society, held at the Queen Elizabeth Hospital on March 21, Professor J. Chassar Moir was elected president, Mr. H. J. Malkin and Mr. S. W. Maslen-Jones vice-presidents, Mr. Samuel Davidson treasurer, Professor H. C. McLaren secretary, and Messrs. H. R. Duval, L. M. Park, A. Wentworth Taylor, and W. Hawkesworth members of council. Papers were read on rupture of the uterus, unusual cases of ectopic pregnancies, hydradenoma of vulva, the passage of foetal parts by the rectum, and labour complicated by pulmonary embolism.

Chelsea Clinical Society

The sixth meeting of the session was held on March 13 at the South Kensington Hotel, 41, Queensgate Terrace, S.W.7, with the president, Mr. Geoffrey Parker, in the chair. A most stimulating discussion on "Some Literary Diagnoses" was opened by Dr. Russell Brain, President of the Royal College of Physicians, and was continued by Mr. Edward Shanks and Mr. Lionel Hale. The next dinner will be on May 8.

Third Annual Report of Faculty of Anaesthetists

In the course of his address given at the annual general meeting before the dinner on March 14 (see *British Medical Journal*, March 24, p. 650), the Dean reported that in the past year 15 Fellows had been elected, making a total of 150, and 101 holders of the diploma in anaesthetics had registered as members, making 1,159 in this category. Most of the year's work had been concerned with education in one form or another, and at the request of the Ministry of Health the Faculty had drawn up criteria for recognition as a consultant. These demand a minimum of seven years' training after qualification, through posts at approved hospitals, the holding of a higher degree, and of a recognized appointment at an approved hospital.

Three a Day

Ninety-three children—an average of three each day—were admitted to Dr. Barnardo's Homes during February.

Pensions and Scholarships for Medical Men

The Royal Medical Foundation of Epsom College has available one Christie and one France pension for necessitous members of the medical profession over 55 years of age. Also available are St. Ann's scholarships for orphan daughters of medical men who have been not less than five years in independent practice in England or Wales.

In Brief

Dr. Macdonald Critchley is visiting Barcelona and Madrid on a lecture tour and afterwards is going to America as visiting professor in neurology at the University of California, San Francisco. He will also lecture in New York, Virginia Beach, Los Angeles, Indianapolis, Winnipeg, and Toronto.

Dr. Ronald Woolmer, senior lecturer in anaesthetics, University of Bristol, is going to Copenhagen this month as senior instructor in charge of the course in anaesthesiology set up by the World Health Organization and open to postgraduates from all European countries.

Wills

Dr. James Leslie Barford, of Redhill, Surrey, left £4,510. He desired that his body be used for scientific research. Subject to the disposal of effects, he left 1/50th part of the residuary estate upon trust for Epsom College, for the encouragement of literature among the boys; 1/50th part of the residuary estate upon trust for King's College Hospital Medical School, to be used if possible to assist students of poor means; and 1/100th part of the residuary estate each to the National Association of Boys' Clubs, Pearson's Fresh Air Fund, and the Royal Medical Benevolent Society. Dr. Alfred Theophile de Mouilpied, of Welwyn Garden City, Herts, left £14,977. Dr. Marjorie Munro, of Lower Rowe, Dorset, left £5,836. Dr. Jessie Downie Granger Evans, of London, N.W.3, left £7,867. Dr. Richard Bertram Johnson, of Burton-upon-Trent, left £11,837. Major-General William Brooke Purdon, Director of Medical Services, B.E.F., 1940, Deputy Director of Medical Services Western Command in 1940–1, and honorary surgeon to the King in 1938–41, left £413. Dr. Ralph William Graham-Yooll, of West Linton, Peebles, left £18,130. Mr. Gervase Edward Newby, of Croydon, left £17,685. Dr. Herbert Stanley French, of Newdigate, Surrey, late physician to H.M. Household and consulting physician to Guy's Hospital, left £32,090.

COMING EVENTS

Traumatic Surgery

An intensive week-end course in traumatic surgery has been arranged by the Institute of Accident Surgery at the Birmingham Accident Hospital, Bath Row, Birmingham, 15, from 9.30 a.m., Friday, to 12.15 p.m., Sunday, April 20–22. The fee for the course is £6 6s., payable to the University of Birmingham, and applications should be sent to the director of postgraduate medical studies, Medical School, University of Birmingham, Edgbaston, Birmingham, 15.

Spa Treatment of Asthma in Children

On April 18 a small reception is being given by the director of La Bourboule Spa, France, at the Ritz Hotel, London (6 p.m. to 7.30 p.m.), to a limited number of doctors and others interested in children's asthma. A short film will be shown. Tickets are strictly limited, and those wishing to attend should apply as soon as possible for an invitation to the secretary of International Help for Children, 43, Parliament Street, S.W.1. This organization has sent parties of London children to La Bourboule for treatment during the last two years, the cost being borne by the spa.

Refresher Course for General Practitioners

A fortnight's refresher course for National Health Service practitioners will start at Edinburgh on May 7. The fee for graduates not claiming expenses from Government sources is 10 guineas. Applications for enrolment should be addressed to the Director of Postgraduate Studies, Surgeons' Hall, Edinburgh, 8. Applicants other than general practitioners should supply particulars of qualifications and postgraduate experience.

Royal Cancer Hospital

On the occasion of the centenary of the Royal Cancer Hospital a Thanksgiving Service will be held at St. Luke's Church, Sydney Street, Chelsea, London, S.W., on Wednesday, May 16, at 4 p.m., when the preacher will be the Very Rev. the Dean of St. Paul's. The same evening, from 5.30 to 7.30 p.m., there will be a reception at the hospital, Fulham Road, S.W., when the guests will be presented to the Duchess of Gloucester.

Marriage Guidance Council

The Fifth Annual Conference of the National Marriage Guidance Council will be held at Harrogate on May 17–21. The subject is "Education for Marriage and Family Life." Full particulars may be obtained from the office secretary, National Marriage Guidance Council, 78, Duke Street, Grosvenor Square, London, W.1.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday

●HUNTERIAN SOCIETY.—At Talbot Restaurant, 64, London Wall, London, E.C., April 16, 7 for 7.30 p.m., annual general (dinner) meeting. "*Hunteriana*," talk by Mr. C. Robert Rudolf.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, London, W.C.—April 16, 5 p.m., "*Speech and Hearing*," by Dr. D. B. Fry.

INSTITUTE OF OPHTHALMOLOGY, Judd Street, London, W.C.—April 16, 5.30 p.m., "*Some Recent Advances in the Treatment of Detachment of the Retina*," by Mr. C. D. Shapland

INSTITUTE OF PSYCHIATRY, Maudsley Hospital, Denmark Hill, London, S.E.—April 16, 5.30 p.m., lecture-demonstration by Dr. E. Stengel.

●ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—April 16, 5 p.m., "*Vesical Diverticula*," by Mr. R. Ogier Ward; 6.15 p.m., "*Glands of the Neck*," by Mr. A. C. Perry.

ROYAL EYE HOSPITAL, St. George's Circus, Southwark, London, S.E.—April 16, 5 p.m., "*Medical Ophthalmology*," by Professor Arnold Sorsby.

Tuesday

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, London, W.C.—April 17, 5 p.m., "*The Medico-Legal Aspects of the Practice of Oto-rhino-laryngology*," by Dr. A. R. French.

PADDINGTON MEDICAL SOCIETY.—At St. Mary's Hospital, Paddington, London, W., April 17, 8.45 p.m., "*Cortisone and A.C.T.H. in Modern Treatment*," by Dr. B. Gottlieb.

●ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—April 17, 5 p.m., "*Flat Foot*," by Mr. T. T. Stamm; 6.15 p.m., "*The Surgery of the Heart*," by Mr. R. C. Brock.

SOCIETY FOR THE STUDY OF ADDICTION.—At Medical Society of London, 11, Chandos Street, Cavendish Square, London, W., April 17, 4 p.m., annual meeting; "*Looking Back Fifty Years*," Presidential Address by Dr. G. W. Smith.

Wednesday

GLASGOW UNIVERSITY: DEPARTMENT OF OPHTHALMOLOGY.—April 18, 8 p.m., "*Anomalies of the Optic Disk*," by Dr. A. Lindsay.

INSTITUTE OF OPHTHALMOLOGY, Judd Street, London, W.C.—April 18, 5.30 p.m., "*Physiology of Vestibular Nystagmus*," by Professor D. Slome.

●ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—April 18, 5 p.m., "*Burns*," by Mr. D. N. Matthews; 6.15 p.m., "*Ectopia Vesicae*," by Mr. E. W. Riches.

ROYAL EYE HOSPITAL, St. George's Circus, Southwark, London, S.E.—April 18, 5.30 p.m., "*The Measurement of Axial Length in the Living Eye*," by Mr. J. F. P. Deller.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE, 28, Portland Place, London, W.—April 18, 3.30 p.m., "*Health Problems in Densely Populated Areas*," by Dr. W. T. O'Donovan. (Free, no tickets required.)

ROYAL MICROSCOPICAL SOCIETY, Tavistock House South, Tavistock Square, London, W.C.—April 18, 5.30 p.m., ordinary meeting.

Thursday

BRITISH INSTITUTE OF RADIOLOGY, 32, Welbeck Street, London, W.—April 19, 8.15 p.m., "*Some Problems of Radiation Protection*," 30th Silvanus Thompson Memorial Lecture by Professor W. V. Meyneord, D.Sc.

LONDON COUNTY MEDICAL SOCIETY.—At St. Olave's Hospital, Lower Road, Rotherhithe, S.E., April 19, 3 p.m., clinical meeting.

●ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—April 19, 5 p.m., "*Carcinoma of the Rectum*," by Mr. H. T. Simmons; 6.15 p.m., "*The Common Bile Duct*," by Mr. R. V. Cooke.

ROYAL EYE HOSPITAL, St. George's Circus, Southwark, London, S.E.—April 19, 5 p.m., "*Myopia: Retinoscopy*," by Dr. T. H. Whittington.

ST. ANDREWS UNIVERSITY.—At Lecture Theatre, Materia Medica Department, Medical School, Small's Wynd, Dundee, April 19, 5 p.m., "*Intersexuality*," by Professor T. N. A. Jeffcoate.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL, Hyde Park Corner, London, S.W.—April 19, 4.30 p.m., "*Psychiatry*," lecture-demonstration by Dr. Desmond Curran.

Friday

BRITISH INSTITUTE OF RADIOLOGY, 32, Welbeck Street, London, W.—April 20, 5 p.m., meeting of medical members; 6.30 p.m., "*The Use of Radioactive Isotopes in Problems Connected with Plastic Surgery*," by Mr. J. N. Barron and Mr. N. Veall, in collaboration with Mr. J. E. Laing and Mr. D. G. Arnott; "*Observations on the Vascular Channels of Tubed Pedicles Using Radioactive Sodium*," by Mr. Fenton Braithwaite, in collaboration with Mr. F. T. Farmer, Ph.D., and Mr. F. I. Herbert.

CENTRAL COUNCIL FOR THE CARE OF CRIPPLES.—At the Goldsmiths' Hall, Foster Lane, Cheapside, London, E.C., April 20, 2.45 p.m., annual general meeting. Address by the Right Honourable Hilary Marquand, M.P., Minister of Health.

FACULTY OF RADIOLOGISTS.—At Royal College of Surgeons of England, Lincoln's Inn Fields, London, W.C., April 20, 2.15 p.m., Diagnosis Section Meeting. "*Sinusitis and Bronchiectasis*," by Dr. J. B. King.

●INSTITUTE OF ACCIDENT SURGERY, BIRMINGHAM.—At Birmingham Accident Hospital, Bath Row, Birmingham, April 20, 9.30 a.m., "*Traumatic Surgery: Upper Limb*," week-end course. (See also April 21 and 22; also Coming Events on this page.)

INSTITUTE OF OPHTHALMOLOGY, Judd Street, London, W.C.—April 20, 5.30 p.m., "*Control of the Intra-ocular Pressure*," by Dr. H. Davson.

LONDON ASSOCIATION OF THE MEDICAL WOMEN'S FEDERATION.—At Royal Free Hospital School of Medicine, 8, Hunter Street, Brunswick Square, London, W.C., April 20, 8.30 p.m., "*Some Important Clinical Aspects of Modern Bacteriology*," by Dr. A. Gibson.

●ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—April 20, 5 p.m., "*Pulmonary Tuberculosis*," by Mr. P. R. Allison; 6.15 p.m., "*Head Injuries*," by Mr. G. F. Rowbotham.

Saturday

●INSTITUTE OF ACCIDENT SURGERY, BIRMINGHAM.—At Birmingham Accident Hospital, Bath Row, Birmingham, April 21, 9 a.m., *"Traumatic Surgery: Lower Limb and Trunk,"* week-end course. (See also April 20 and 22; also Coming Events, p. 830.)

SOUTH-EAST METROPOLITAN REGIONAL TUBERCULOSIS SOCIETY.—At Lenham Sanatorium, Lenham, April 21, 10.30 for 11 a.m., *"Clinical Aspects of Thiosemicarbazone in Pulmonary Tuberculosis,"* by Dr. R. Livingstone; *"Biochemical Aspects of Thiosemicarbazone in Pulmonary Tuberculosis,"* by Dr. E. R. Jones; *"Primary Lesions,"* by Dr. Ruth Dingley.

Sunday

●INSTITUTE OF ACCIDENT SURGERY, BIRMINGHAM.—At Birmingham Accident Hospital, Bath Row, Birmingham, April 22, 9.30 a.m., *"Traumatic Surgery: Open Wounds,"* week-end course. (See also April 20 and 21; also Coming Events, p. 830.)

APPOINTMENTS

APSEY, G. R. M., M.D., D.P.H., Regional Medical Health Officer, Health Region No. 3, Saskatchewan, Canada.

CRICHTON ROYAL, Dumfries.—*Crichton Fellowships:* P. Rowsell, M.B., B.Chir., M.R.C.P.; J. Harrington, M.D., D.P.H., D.I.H.

CROSS, RAYMOND GERARD, M.D., M.A.O., D.P.H., M.R.C.O.G., F.R.C.P.I., Assistant Gynaecologist, Meath Hospital and County Infirmary, Dublin.

CURRAN, ANDREW P., M.B., Ch.B., D.P.H., Deputy Medical Officer of Health and Deputy School Medical Officer, Borough of Luton.

DOYLE, JOSEPH IGNATIUS, M.B., B.Ch., Medical Officer, Coolattin Dispensary District, Co. Wicklow, Eire.

DUNCAN, ERIC H. WEIR, M.B., Ch.B., D.P.H., Medical Officer of Health, Greenock.

FOREMAN, H. M., M.B.E., M.B., Ch.B., M.R.C.P., Physician-Superintendent (Consultant), Sully Hospital, Welsh Regional Hospital Board.

HASTILOW, IRENE M. D. F. C., M.B., Ch.B., D.P.H., D.C.H., D.Obst.-R.C.O.G., Medical Officer of Health for Saffron Walden Borough and Saffron Walden Rural District, and Assistant County Medical Officer for Essex.

HORTON, E. H., M.B., B.Ch., Assistant Chest Physician (S.H.M.O.), Brecon and Radnorshire Area.

HOSPITAL FOR SICK CHILDREN, Great Ormond Street, London, W.C.—*Assistant Medical Registrars (Registrar Grade)*, P. J. N. Cox, B.M., M.R.C.P., D.C.H., D. H. Garrow, B.M., M.R.C.P., J. Luder, M.D., M.R.C.P., D.C.H., R. G. Welch, M.D., M.R.C.P. *Part-time Surgical Registrars (Senior Registrar Grade)*, T. Rowntree, M.S., F.R.C.S., I. F. Rose, F.R.C.S.

JEFFERY, C. C., F.R.C.S., Consultant Orthopaedic Surgeon in Exeter Clinical Area, South-western Regional Hospital Board.

PARKER, WILLIAM SHEPHERD, M.B., Ch.B., D.P.H., D.I.H., Medical Officer of Health, Brighton County Borough.

ROGAN, JOHN M., M.D., F.R.C.P.Ed., D.P.H., Chief Medical Officer, National Coal Board.

ROSS, HENRY A., M.B., Ch.B., D.P.H., Physician-Superintendent, South Wales Sanatorium, Talgarth, Breconshire.

SAMBROOK, D. K., M.B., B.S., F.R.C.S., D.M.R.T., Consultant Radiotherapist, Glantawe Hospital Management Committee Group, Swansea.

SOUTH-WESTERN REGIONAL HOSPITAL BOARD.—*Consultant Radiologist in South Somerset Clinical Area*, John Winter, M.B., Ch.B., M.Rad., D.M.R.D. *Senior Surgical Registrar in West Cornwall Clinical Area*, C. B. O'Carroll, M.B., B.S., F.R.C.S.Ed.

STEWART, JOHN BERKLEY, M.B., Ch.B., D.Phys.Med., Consultant in Physical Medicine, Cirencester, Swindon, and Pewsey Hospital Management Committees.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Howat.—On April 2, 1951, to Margaret (formerly Harker), wife of Dr. James Howat, 3, Tankerville Terrace, Newcastle-upon-Tyne, a daughter.

Mann.—On March 15, 1951, at Aberdeen Maternity Hospital, to Dr. and Mrs. A. B. Mann (Irene Menzies), "Lochnagar," Cults, Aberdeenshire, a son.

Raper.—On March 31, 1951, at Kampala, Uganda, to Doris, wife of Dr. Alan Raper, a son.

Stuart-Harris.—On March 28, 1951, at the Hammersmith Hospital, to Marjorie, wife of Professor C. H. Stuart-Harris, M.D., F.R.C.P., a son.

MARRIAGES

Beveridge—Pinney.—On March 29, 1951, at the Parish Church, Sidmouth, Devon, Dr. T. S. Beveridge to Miss Cynthea Pinney, S.R.N.

DEATHS

Craig.—On March 24, 1951, at Roseville, Gatehouse-of-Fleet, Kirkcudbrightshire, Alexander Currie Carruthers Craig, M.B., Ch.B., aged 56.

Farquharson.—On March 25, 1951, at The Grange, Wetheral, Carlisle, William Frederick Farquharson, M.D., aged 84.

Furness.—On March 24, 1951, at Clarehaven, Melton Mowbray, Harold Sydney Furness, M.D., aged 67.

Liddell.—On March 22, 1951, at 30, Greenbank Drive, Edinburgh, John Liddell, M.B., C.M., late of Errol, Perthshire.

McDougall.—On March 24, 1951, at a Bournemouth nursing-home, John Tiley Montgomery McDougall, 8, Dunkeld Road, Bournemouth, aged 75.

Messiter.—On March 26, 1951, at 3, Ednam Road, Dudley, Worcs, Cyril Cassan Messiter, M.R.C.S., L.R.C.P.

Owles.—On March 20, 1951, at his home, 14, Whitehall Road, Rhos-on-Sea, Colwyn Bay, Wilfred Harding Owles, D.M., M.R.C.P.

Sprague.—On March 21, 1951, at his home, 4, Clarence Street, Gloucester, Francis Henry Sprague, M.R.C.S., L.R.C.P.

Symes.—On March 25, 1951, at 6, Pembroke Vale, Clifton, Bristol, John Odery Symes, M.D., D.P.H., aged 83.

Wigham.—On March 22, 1951, at Dublin, Joseph Theodore Wigham, M.D., F.R.C.P.I., of Edenvale, Conyngham Road, Dublin, aged 76.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Foetal Damage from X Rays

Q.—*(1) What is the mechanism of irradiation damage to the foetus? (2) Should a woman be allowed to have children after she has had therapeutic irradiation to the abdomen or pelvis? If so, what criteria of dosage, site, etc., should be applied in deciding in a particular case?*

A.—(1) If a woman is irradiated during pregnancy damage to the foetus will depend on whether the foetus receives either direct or scattered radiation; if it does, the effects will be those following irradiation of any young growing tissues. There is at present no evidence that chemical substances produced by irradiation of maternal tissues reach and damage the foetus.

(2) If a woman has had therapeutic irradiation for a malignant tumour in the abdomen or pelvis it is most unlikely that she will have children. If she has had small doses of irradiation for a benign condition there is little evidence that such treatment results in a real increase in the proportion of abnormal pregnancies, but the possibility of genetic changes due to irradiation of the ova cannot be ignored.

Sulphones in Leprosy

Q.—*How effective are sulphones in the treatment of leprosy? How are they given?*

A.—A number of sulphone derivatives (e.g., "promanide" intravenously; "diasone," "promizole," "sulphetrone" orally) have been used in the treatment of lepromatous leprosy. These drugs almost invariably arrest the progress of the lepromatous lesions and prevent the development of new lesions; in most cases they cause retrogression and even disappearance of the lepromatous lesions, with diminution of the numbers of bacilli in them sometimes to such an extent that the bacilli can no longer be recovered. Apparent "cure" has therefore been reported in a number of cases; but in an extremely chronic infection of this type, where evidence of the presence of the causative organisms rests solely on their recognition on microscopical search, it is very difficult to say when sterilization of the infection has been achieved. Claim to "complete success as a cure" is therefore not warrantable at least until many years of close study and repeated examination support it.

It has always seemed probable that the derivatives of diamino-diphenylsulphone (D.D.S.) are not active as such but that they owe their activity to hydrolysis with liberation of the parent substance. D.D.S. was stated initially to be too toxic for use in man; with suitable modification in dosage it now is used by many workers; the results of treatment with it appear to be at least as good as those obtained with the more expensive and complicated compounds. The maximum tolerated dose of D.D.S. by mouth is stated to range from 100 to 300 mg. a day. A dose of 30 to 50 mg. of D.D.S. a day is said to be effective; for mass treatment in Nigeria up to 400 mg. are given twice a week.

Diasone is given orally in doses of up to 2 g. daily; promizole or sulphetrone orally in doses up to 6 or 8 g. daily, though 2 to 4 g. daily have given good therapeutic results. In every case the initial dosage of D.D.S., or its derivatives, must be very small; it is gradually increased, with caution, to the full dosage over a period of not less than about three months. Precipitate increase in dosage may cause lepra fever and a flare-up of the disease; the serious toxic effects of the drug include the development of a severe anaemia; this must constantly be watched for. Reduction

in the dosage of the drug, or even its suspension, may be necessary in these events. As habituation is established the risk of toxicity diminishes. Treatment should continue over many months, or even many years, with or without intermissions of a week or two from time to time, as appears necessary in the individual case

Arm Girth and Blood-pressure Readings

Q.—*Does excessive girth in the arm affect the accuracy of blood-pressure readings; if so, in which direction and to what extent?*

A.—Using a standard blood-pressure cuff (9×5 in.—23.9×12.7 cm.) excessive girth of the arm is likely to result in a reading that is too high. This general principle is well illustrated by the use of the standard cuff on the thigh when attempting to take blood-pressure readings in the legs. These are invariably too high when compared with direct intra-arterial records. To a certain extent the difficulty can be overcome by using a larger cuff. When a larger cuff is used on a normal arm the reading obtained is likely to be too low. Similarly, the standard cuff used on the thin arm of a child also tends to give readings that are too low. Unfortunately it is very difficult to correct these errors by using suitable cuffs for each patient, because without experiment it is almost impossible to know what size cuff in any individual will give the most accurate reading. It is not a bad policy, however, to carry three sizes of cuff, large, standard, and small. Alternatively, one can simply bear the principle in mind. If one is aware of a likely error there is less chance of being seriously misled.

Nutritional Value of Gelatin

Q.—*After ox bones, etc., have been boiled in water for some hours the whole, on cooling, sets in a firm jelly, and presumably this is due to osseous gelatin. What value is this jelly to starved persons or patients suffering from protein depletion?*

A.—Gelatin from any source is deficient in the amino-acids tryptophan and tyrosine, and was at one time considered to be of little nutritional value. Rats are quite unable to grow when given gelatin as their sole source of protein. Experiments by Chick, however, have shown that when two defective proteins are eaten together one may often make good the deficiency of the other. Thus she has clearly demonstrated that the gelatin of beef tea and protein of bread have a much greater nutritional value when taken together than when consumed separately. The jelly from bones should therefore be of considerable value to starved or protein-deficient persons if received in adequate quantities in conjunction with a vegetable protein capable of compensating for its defects. As a source of protein the combination would still not equal milk or meat, but ease of digestion might well outweigh this defect in the first stages of the rehabilitation after starvation.

Acute Thyroiditis and Influenza

Q.—*I have seen a case of acute thyroiditis following influenza in the recent epidemic. Is this a recognized complication of influenza, and, if so, how frequent is it? How is it caused, and what is the prognosis?*

A.—Acute thyroiditis is a very rare condition. It has been recorded in influenza, but so infrequently that it could scarcely be regarded as a recognized complication. It has also been described in scarlet fever, typhoid fever, malaria, and septicaemia: it may result by extension from an infected wound of the neck or from adjacent cellulitis or abscess. In typhoid fever, the typhoid bacillus has been cultured from the pus, with or without other pyogenic organisms, suggesting that the infection is blood-borne. In influenza, the cause would most probably be one of the secondary invaders and not the influenza virus. According to most writers the condition usually resolves, but it may go on to pus formation, and there is then danger of invasion of the cellular planes of the neck. Modern chemotherapy should control the condition.

Pethidine Addiction in Gout

Q.—*A man of 38 who has gout insists on 200 mg. pethidine daily to control the pain. Is this a case of pethidine addiction, and, if so, what should be done about it?*

A.—Certainly this is a case of pethidine addiction. Gout never justifies *daily* administration of powerful analgesics. No addict can be treated satisfactorily at home. You should insist on his entering a hospital or nursing-home. The drug should then be fully withdrawn within three days and the patient kept under observation in the institution for a month. No details are given in respect of the gout, and therefore this aspect of the case cannot be dealt with.

Dipsomania in the Aged

Q.—*What is considered the best method of treating a dipsomaniac man aged 78 at home? Would "antabuse" be any good?*

A.—Surely the point here is that either the dipsomaniac tendencies create a social problem or they do not. If they do, is it right and proper that the patient should go on being treated at home? If there is a real problem he would best be put in a home for the aged, where he could be adequately supervised; or if he is a well-off man he could be cared for by having a male nurse in personal attendance. I would certainly not suggest "antabuse" in this case. The treatment is physiologically depressing and would not be tolerated by a man of this age.

Syphilis in Women

Q.—*Syphilis is said to be a milder disease in women than in men. Is this true, and, if so, why?*

A.—All observers are agreed that syphilis is a much milder disease in the female than in the male, the routine blood test often being the only method of diagnosis even in women who have infected their sexual partners or offspring. Acute manifestations are, of course, sometimes seen in women, especially before puberty or after the climacteric, more rarely during the reproductive period. It will also be found that females, much more frequently than males, suffering from latent syphilis or late manifestations (cardiovascular or nervous) give no history of signs of primary or secondary stages.

The benign course of syphilis in the female has been attributed to the beneficial effects of pregnancy, but, as Moore states, "recent experimental studies have shown that the female sex hormones are probably equally responsible." The biochemistry in both pregnancy and menstruation may, as suggested by some workers, cause reactions similar to those following non-specific shock therapy.

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